イラリス皮下注用 150 mg

に関する資料

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1.5 起源又は発見の経緯及び開発の経緯

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略号一覧

略号	省略していない表現 (英)	省略していない表現 (日)
AUC	area under the drug plasma (serum/blood) concentration-time curve	血漿（血清/血液）中薬物濃度-時間曲線下面積
CAPS	cryopyrin-associated periodic syndrome	クリオピリン関連周期性症候群
crFMF	colchicine resistant Familial Mediterranean Fever	コルヒチン抵抗性家族性地中海熱
CRP	c-reactive protein	C 反応性蛋白
EU	European Union	欧州連合
HIDS	Hyper IgD Syndrome	高 IgD 症候群
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use	日米 EU 医薬品規制調和国際会議
IG	immunoglobulin	免疫グロブリン
IL	interleukin	インターロイキン
MKD	Mevalonate Kinase Deficiency	メバロン酸キナーゼ欠損症
NSAID	non-steroidal anti-inflammatory drug	非ステロイド性抗炎症薬
QOL	quality of life	生活の質
SJIA	Systemic Juvenile Idiopathic Arthritis	全身型若年性特発性関節炎
TNF	Tumor necrosis factor	腫瘍壊死因子
TRAPS	TNF Receptor-Associated Periodic Syndrome	TNF 受容体関連周期性症候群

用語の定義一覧

用語	定義
再燃	再燃は，臨床的再燃と血清学的再燃が同時に認められた場合と定義した。 • 臨床的再燃：医師による全般評価が軽度以上 • 血清学的再燃：CRP 30 mg/L 以上 Day 15 に index flare の寛解が得られた被験者は，Day 15 以降にこの定義を適応した。

1 起原又は発見の経緯

カナキヌマブはノバルティス社が創製したヒトインターロイキン（interleukin，以下 IL）-1β に対する遺伝子組換えヒト免疫グロブリン G（immunoglobulin G）1 モノクローナル抗体であり，IL-1β に結合して IL-1β 受容体への結合を阻害し，その活性を中和する。

IL-1β は，炎症性サイトカインの一つであり，一般的に，インターロイキン等のサイトカイン又は Toll 様受容体リガンドによって誘導され，プロ IL-1β として産生されるが，IL-1β に変換された後に細胞外へ放出される。この IL-1β の産生には，インフラマソームという蛋白質複合体が関与している。

ノバルティス社は 2005 年よりクリオピリン関連周期性症候群（cryopyrin-associated periodic syndrome，以下 CAPS）等の IL-1β が関連すると考えられる炎症性疾患を対象としたカナキヌマブの臨床開発に着手した。

2 周期性発熱症候群について

自己炎症性疾患は，自然免疫の異常により自己免疫や感染症の直接的な関与なしに全身性の炎症が起こる疾患の一群として知られている。その中でも周期性発熱症候群は，必ずしも規則的ではないが，間欠的に発熱を繰り返す希少な遺伝性自己炎症疾患のグループであり，CAPS，家族性地中海熱（Familial Mediterranean Fever，FMF），TNF 受容体関連周期性症候群（TNF Receptor-Associated Periodic Syndrome，TRAPS）及びメバロン酸キナーゼ欠損症（Mevalonate Kinase Deficiency，MKD；文献等では高 IgD 症候群 Hyper IgD Syndrome，HIDS と呼称されることもある）が含まれる。主な特徴は共通して，日常生活に支障を来すほどの高熱を伴う全身性炎症発作を繰り返し，炎症性サイトカインの標的となる臓器及び器官に特有の徴候及び症状，すなわち，漿膜炎，好中球性皮疹，粘膜潰瘍，関節痛・関節炎，無菌性髄膜炎・頭痛等を伴うことである。発熱に CRP，血清アミロイド A 等の炎症マーカーの増加を伴う（楠原 2010a，Piram et al. 2011，ter Haar et al. 2013）ことも 3 つの疾患に共通である。

周期性発熱症候群に共通する臨床症状として特徴的な高熱を伴う全身性炎症の発作は，これらの患者の生活の質に著しい影響を及ぼす。したがって，多くの患者が発作の再燃予防と，症状の軽減又は発作の持続期間短縮に有効な治療薬を必要としている（Hoffman and Simon 2009）。治療について，CAPS の治療薬としてはカナキヌマブが既に市販されているが，FMF，TRAPS，MKD/HIDS では国内で有効性や安全性が検証され，承認されている治療薬はない。FMF，TRAPS，MKD/HIDS の治療には，主に経口抗炎症薬（NSAID やアセトアミノフェン等の解熱薬）や副腎皮質ステロイド（以下，ステロイド）が多く使用されており，解熱や発熱を伴う症状の軽減にはある程度の効果を示す。しかし，再燃の予防や発作の持続時間を短縮することはできない。3 つの疾患の中で，FMF に対してはコルヒチンの有効性が確立しており，FMF の再燃を抑制するとともに生命を脅かすアミロイドーシスの発症リスクを低減できることが知られている。しかし，

コルヒチン抵抗性あるいは不耐容の FMF（colchicine resistant Familial Mediterranean Fever，以下 crFMF）患者も存在し，これらの crFMF 患者には有効な他の治療が必要とされている。また，高用量のコルヒチン投与を必要とする患者では，下痢，腹痛，嘔吐等の副作用が問題となる。以上のとおり，周期性発熱症候群のうち，FMF，TRAPS 及び MKD/HIDS に対する有効な治療選択肢は極めて限られている。再発性の発熱を伴う全身性炎症を良好にコントロールでき，長期に安全に使用できる治療法の確立が望まれている。

2.1 家族性地中海熱（FMF）について

2.1.1 FMF の定義，診断基準及び患者数

FMF の臨床的特徴は，突然 38 度以上の高熱を発し，短い発熱を周期的に繰り返すことである。発熱は自然に解熱し，発熱の間隔は 1 ヵ月ごとが典型的であるが，患者によってさまざまである。発熱に伴って多様な漿膜炎症状（腹膜炎，胸膜炎，髄膜炎，関節滑膜炎等）があらわれる。腹膜炎，胸膜炎は激しい痛みを伴うことがあり，胸水貯留を認めることもある。滑膜炎は，膝関節，足関節等の下肢の単関節で発症することが多く，関節水腫を伴うことがある。また，頻度は少ないが，丹毒様紅斑（発熱を伴い，発赤，圧痛を伴う境界の明瞭な膨降した皮疹），心外膜炎，無菌性髄膜炎等の随伴症状がみられることもある（右田，上松 2011，難病情報センター 2012c，厚生労働省 2015c）。好発年齢は 5～20 歳であるが，幼児期に徴候がみられることがあり，成人でも発症する。病態形成には，MEFV（Mediterranean fever）遺伝子産物である Pyrin 蛋白の変異が関与するが，Pyrin 蛋白の欠損又は異常による発症機序の詳細は明らかにされていない。

FMF の診断には，外国では Tel-hashmer criteria（Livneh et al. 1997）が用いられている。国内では，厚生労働省研究班による Tel-hashmer criteria を改変した診断基準が提案されている。国内の診断基準では，38 度以上の発熱に加えて，随伴症状の存在，コルヒチンによる発作の消失又は軽減を組み合わせて，臨床的に FMF 典型例を診断する。一方，診断基準の一部の項目にしか該当しない場合には，MEFV 遺伝子解析を行い，変異の有無を確認する。これらの点は Tel-hashmer criteria と異なるが，診断上の本質的な違いはない。

FMF は周期性発熱症候群の中で最も発症頻度の高い疾患であり，患者数は全世界で約 10 万人（Onen 2006），本邦においては患者総数は約 300 人であると推測されている（右田，上松 2011）。

2.1.2 FMF に対する治療の現状

FMF に対しては，国内未承認であるものの，コルヒチンの有効性が確立しており，FMF の発作を抑制するとともに生命を脅かすアミロイドーシスの発症リスクを低減できることが知られている。厚生労働省難治事業研究班報告では，FMF の診断が確定した場合コルヒチンを投与すべき

であるとされており，ほとんどの日本人 FMF 患者にコルヒチンが投与されていると考えられる。コルヒチンの日本人 FMF に対する有効率は 90%前後であり（厚生労働省 2015c），10%前後の患者はコルヒチン抵抗性あるいは不耐容の FMF（colchicine resistant Familial Mediterranean Fever，以下 crFMF）患者であると考えられ，このような患者では他の治療を必要としている。なお，コルヒチンの FMF に対する使用は，平成 28 年 2 月 3 日実施の第 26 回医療上の必要性の高い未承認薬・適応外薬検討会議にて公知申請することが認められ，平成 28 年 9 月 28 日に承認された。

2.2 TNF 受容体関連周期性症候群（TRAPS）について

2.2.1 TRAPS の定義，診断基準及び患者数

TRAPS は，I 型 TNF 受容体（以下，TNFRI）をコードする遺伝子である *TNFRSF1A* の異常によって引き起こされる。38 度を超える発熱が数週間持続する発作を平均 5～6 週間の間隔で繰り返す。随伴症状として，多くの患者で関節痛，筋肉痛及び皮疹がみられる。また，その他に，眼症状（結膜炎，眼窩周囲浮腫），腹痛等の消化器症状を伴う場合がある。発症年齢は，乳児期から成人まで幅広いが，20 歳未満で発症する例が多い（楠原 2010b，厚生労働省 2015a）。

診断基準について，Hull らが提唱した診断基準が国際的に参照されており（Hull et al. 2002），厚生労働省研究班が示した診断基準（厚生労働省 2015a）も概ね共通である。すなわち，臨床症状，家族歴，及び発症年齢に基づき TRAPS 疑い例を特定し，さらに確定診断のために遺伝子検査を行う。

TRAPS 患者数は，欧州が最も多く，150~230 名報告されており（Aganna et al. 2003，Toplak et al. 2012，Lachmann et al. 2014），国内では 10 数名～30 数名と極めて少ない（楠原 2010b，難病情報センター 2012a）。

2.2.2 TRAPS に対する治療の現状

国内外ともに TRAPS を適応疾患として承認されている医薬品はなく，TRAPS の治療法としては，NSAIDs は解熱剤としては有効であるが，筋肉痛や腹痛等の随伴症状に対する効果は弱い。ステロイドによく反応することが本疾患の特徴の 1 つであり，成人でプレドニゾロン 20~40 mg/日の内服で発熱等の症状を抑制することができる。ステロイドを投与した場合，開始当初の劇的な炎症抑制効果が時間とともに弱まり，より多量，頻回のステロイド投与が必要となる。（楠原 2010a）

2.3 メバロン酸キナーゼ欠損症（MKD）／高 IgD 症候群（HIDS）について

2.3.1 MKD/HIDS の定義，診断基準及び患者数

MKD/HIDS は，メバロン酸キナーゼ遺伝子の変異によって，メバロン酸キナーゼ活性が欠乏することで引き起こされる（van der Hilst et al. 2005）。乳幼児期に発症し，繰り返す発熱と，腹痛（しばしば激痛），下痢，嘔吐等の消化器症状，関節症，皮疹等を伴う。ほとんどの患者でリンパ節腫脹がみられ，約半数の患者でアフタ性口内炎，時に肝肥大や脾腫を伴う（van der Hilst et al. 2005，酒井，平家 2012a）。また，脾腫，溶血性貧血，血小板減少等の血液疾患，炎症性腸疾患，ブドウ膜炎等の炎症疾患，糸球体腎炎，糖尿病等，さまざまな慢性疾患の合併が報告されている（厚生科学審議会 2015）。

MKD は，血清 IgD が高値を示す患者が多いことから，当初 HIDS と命名された。しかし，IgD の上昇を認めないことも多く（難病情報センター 2012b），近年は本疾患の本態はメバロン酸キナーゼ活性の低下であると考えられている。そのため，臨床現場ではいずれの疾患名も使用されている。

診断の手順は国内外で概ね共通である。まず，臨床症状に基づき疑わしい患者を特定し，次に，発熱発作時の尿中メバロン酸値の測定，メバロン酸キナーゼ遺伝子解析を行い，さらに国内ではメバロン酸キナーゼ酵素活性を測定する（Hoffman and Simon 2009，厚生労働省 2015b）。

患者数は，欧州では約 100 名（Toplak et al. 2012），国内における患者は 4 家系 6 名（酒井，平家 2012a）が報告されている。診断の確立していない希少疾患であり，潜在的な患者が他に存在する可能性があるがその数は極めて少ないと想定される。

2.3.2 MKD/HIDS に対する治療の現状

国内外ともに MKD/HIDS を適応疾患として承認されている医薬品はなく，また，具体的な治療指針はいまだ定まっていないが，発作時のステロイド薬の短期的全身投与が多くの症例で有効とされている（酒井，平家 2012a）。

2.4 本剤の FMF，TRAPS，MKD/HIDS に対する治療上の位置付け

前項までに述べたとおり，FMF，TRAPS，MKD/HIDS いずれに対しても国内で有効性及び安全性が検証され承認された治療薬はない。また，種々の薬剤による治療が試みられているが，現時点でこれらの疾患の治療法は確立されていない。

FMF，TRAPS，MKD/HIDS の患者は，発熱発作のたびに学校や仕事を休まざるを得ないために社会的 QOL が著しく障害されている。また，炎症が長期に持続するとアミロイドーシスを発症し生命を脅かす（Hoffman and Simon 2009）。3 疾患の中でも，MKD/HIDS は乳幼児期に発症した

場合，発育早期から持続する炎症と長期治療に伴う副作用のためにさまざまな身体・精神障害を伴う。FMF，TRAPS ではアミロイドーシスが予後に影響することが知られているが，特に FMF では，アミロイドーシスを合併する割合が高い。アミロイドーシスの予防のためには，早期診断，早期治療介入が望まれる（van der Hilst et al 2005，右田，上松 2011）。

以上より，再発性の発熱を伴う全身性炎症を良好にコントロールでき，長期に安全に使用できる治療法の確立が望まれている。

3 開発の経緯

カナキヌマブは，CAPS 患者を対象に実施した臨床試験においてさまざまな炎症症状が速やかに改善され，その効果が長時間持続することが示された。これにより CAPS 治療薬として，2009 年 7 月にイラリス（Ilaris）という製品名で米国で最初に承認され，2011 年 9 月には国内でも承認された。2016 年 9 月現在，世界約 70 ヵ国で承認をされている。

また，米国及び EU で全身型若年性特発性関節炎（Systemic Juvenile Idiopathic Arthritis，以下 SJIA）及び痛風に対する効能追加申請が行われ，SJIA は 2013 年 5 月に米国，2013 年 8 月に EU で承認され，痛風は 2013 年 2 月に EU で承認された。現在，SJIA 患者を対象に国内第 III 相臨床試験を実施中である。

本承認事項一変承認申請の FMF，TRAPS 及び MKD/HIDS は，EU を含む 12 ヵ国で追加承認申請をしており，さらに 3 ヵ国で追加承認申請を予定している。なお，米国では 2016 年 9 月 23 日に FMF，TRAPS 及び MKD/HIDS の適応が承認された。日本国内では，2014 年 1 月 10 日に「メバロン酸キナーゼ欠乏症」，「TNF 受容体関連周期性症候群」及び「家族性地中海熱」を対象として希少疾病用医薬品の指定申請を行い，2014 年 5 月 13 日に希少疾病用医薬品の指定を受けた［指定番号（26 薬）第 334 号，335 号，336 号］。

本承認事項一変承認申請における開発の経緯図を Figure 3-1 に示す。

Figure 3-1 開発の経緯図

試験項目＼年			2010 (H22)	2011 (H23)	2012 (H24)	2013 (H25)	2014 (H26)	2015 (H27)	2016 (H28)
生物薬剤学	プレフィルドシリンジ製剤と凍結乾燥剤の生物学的同等性試験	海外 / A2104試験	[redacted]						
臨床	比較対照試験	国内 / N2301試験							
治験相談		医薬品第Ⅱ相試験終了後相談（オーファン以外）							

3.1 臨床データパッケージ

前述のとおり，FMF，TRAPS，MKD/HIDS の各疾患は国内の患者数は非常に限られており，国内外の診断・治療体系に大きな違いはない。さらに，過去に実施した臨床試験結果から，日本人健康被験者又は CAPS 患者にカナキヌマブを投与した時の薬物動態及び薬力学では，日本人と外国人で明らかな人種差は認められなかった。

臨床データパッケージは次のとおり構成した。評価資料は，バイアル入り液剤と凍結乾燥製剤を比較した生物学的同等性試験（A2104 試験），日本人患者も参加し有効性及び安全性の確認を目的として実施した国際共同第 III 相試験（N2301 試験）の 2 試験とした。参考資料は，海外で実施された crFMF，TRAPS，MKD/HIDS に対する効果を探索する 4 つの Proof of concept 試験（D2203 試験，D2402 試験，D2204 試験，DTR01 試験），長期安全性を確認するため，本申請の適応症と同じく周期性発熱症候群に属する CAPS 患者を対象とした 5 つの臨床試験（D2308 試験，D2201 試験，D2304 試験，A2102 試験，D2306 試験），さらに現在日本人 HIDS 患者を対象に実施されている臨床研究で構成した。

CAPS はクリオピリン関連遺伝子（*NLRP3*）の変異によって引き起こされる点が FMF，TRAPS，MKD/HIDS と異なるものの，周期性発熱症候群に属する疾患であり IL-1β の過剰産生が慢性的な炎症反応や進行性の組織障害を引き起こす点ではこれら 3 疾患と類似した疾患である。また，CAPS を対象とした臨床試験では，カナキヌマブを 150 mg～600 mg（体重 40 kg 以下では 2～8 mg/kg）の用量範囲で 4～8 週間隔で投与しており，crFMF，TRAPS，MKD/HIDS に対して検討した用法用量はこの範囲に含まれる。よって CAPS 患者を対象とした 5 つの臨床試験は，カナキヌマブの周期性発熱症候群に対する安全性評価の参考になり得ると考え臨床データパッケージに含めた。

また，現在国内で MKD/HIDS（1 名）を対象にカナキヌマブ（最高用量 8 mg/kg）を投与する臨床研究が実施されており，その中間報告書を参考資料として臨床データパッケージに含めた。

3.1.1 生物学的同等性試験（A2104 試験）

現在，国内ではカナキヌマブの凍結乾燥製剤が市販されている。さらに，カナキヌマブの同一製剤処方の注射液をバイアルに充填した製剤（以下，バイアル入り液剤）及びシリンジに充填された製剤（以下，プレフィルドシリンジ製剤）を開発中である。

crFMF，TRAPS，及び MKD/HIDS を対象とした第 III 相試験（N2301 試験）では，バイアル入り液剤を使用した。また，健康被検者を対象としてプレフィルドシリンジ製剤 と市販の凍結乾燥製剤を単回皮下投与したときの生物学的同等性を検証した生物学的同等性試験（A2104 試験）を実施した。

外国人健康被検者を対象として，プレフィルドシリンジ製剤と市販の凍結乾燥製剤を単回皮下投与したときの生物学的同等性を検討した（2.7.1，A2104 試験）カナキヌマブの Cmax 及び AUClast の幾何平均値の比（プレフィルドシリンジ製剤／凍結乾燥製剤）の 90%信頼区間は後発

医薬品の生物学的同等性試験ガイドライン（2012 年 2 月 29 日，薬食審査発 0229 第 10 号）の生物学的同等性の基準（幾何平均値の比の 90%信頼区間：0.8～1.25）を満たしたことから，プレフィルドシリンジ製剤は市販の凍結乾燥製剤と生物学的に同等と判断した。

また，プレフィルドシリンジ製剤とバイアル入り液剤の組成は同一であり，凍結乾燥製剤とバイアル入り液剤については，同等／同質であることが確認されている（2.7.1-3.1 項）。したがって，臨床試験で用いられた凍結乾燥製剤，プレフィルドシリンジ製剤，及びバイアル入り液剤の 3 製剤は生物学的に同等であると考える。

3.1.2 crFMF，TRAPS，HIDS 患者を対象とした第 III 相試験（N2301 試験）

N2301 試験は，crFMF，TRAPS，HIDS を対象とした，多施設共同，ランダム化，二重盲検，プラセボ対照，並行群間比較であり，日本を含む国際共同試験として実施した。なお，FMF では既に有効性が確立されているコルヒチンがあるため，本試験では crFMF を対象とした。また MKD/HIDS の疾患名については 2.3.1 項で述べたとおり，N2301 試験計画当時には 血清 IgG 高値を示す という疾患の特徴から HIDS が用いられていたため，対象疾患名を HIDS として実施した（以下，本試験の対象患者を示す場合は HIDS と記載）。試験期間は計 4 期で構成され，スクリーニング期（最長 12 週間），プラセボとの比較でカナキヌマブの有効性を確認する二重盲検期（ランダム化，16 週間），効果の持続を評価する投与中断・投与頻度低減期（再ランダム化，二重盲検，24 週間），長期安全性を評価する非盲検期（72 週間）を設け，カナキヌマブの有効性及び安全性を検証し，臨床推奨用法用量を検討した。N2301 試験には，全体でランダム化群 181 名（crFMF：63 名，TRAPS：46 名，HIDS：72 名），非ランダム化群 4 名（crFMF：2 名，HIDS：3 名）が組入れられ，そのうち日本人被験者数は，ランダム化群 8 名［ACZ885：2（crFMF：0，TRAPS：2，HIDS：0），プラセボ：6（crFMF：1，TRAPS：4，HIDS：1）］，非ランダム化群 3 名（crFMF：2，TRAPS：0，HIDS：1）であった。N2301 試験は本承認申請時点で実施中であり，本項には二重盲検期を完了した 16 週中間集計の結果を示す。

有効性

N2301 試験の 16 週の寛解率を主要評価項目として，プラセボ群に対する 150 mg 4 週間隔投与群の優越性が，crFMF，TRAPS，HIDS のいずれの疾患でも示された。16 週の寛解率（150 mg 4 週間隔投与群，プラセボ群）は，crFMF（61.29%，6.25%），TRAPS（45.45%，8.33%），HIDS（35.14%，5.71%）であり，寛解率の投与群間差（150 mg 4 週間隔投与群 − プラセボ群）は crFMF，TRAPS，HIDS 各疾患でそれぞれ，55%，37%，29%であった。カナキヌマブの効果は速やかに発揮され，Day 15 の早期から医師による全般評価，CRP，血清アミロイド A の減少がみられ，二重盲検期終了時までその減少が維持された。日本人部分集団でも，医師による全般評価，CRP，血清アミロイド A の改善が認められた。カナキヌマブは既存治療によっても十分な効果が

得られない crFMF，TRAPS， HIDS に対し，症状の再燃をコントロールし，全身性の炎症を改善することが確認された。

安全性

N2301 試験で crFMF，TRAPS，HIDS に対してカナキヌマブを投与した際の安全性プロファイルは，カナキヌマブの既承認の適応症に対する使用経験から副作用であることが報告されているものと同様であり，crFMF，TRAPS，HIDS で新たに認められたものはなかった。死亡の報告はなかった。重篤な有害事象，治験薬の投与中止に至った有害事象，休薬又は減量を要した有害事象の発現はわずかであった。重篤な有害事象，治験薬の投与中止に至った有害事象，休薬又は減量を要した有害事象の多くは，処置により消失した。有害事象の主な内容は，crFMF，TRAPS，HIDS とも共通して鼻咽頭炎及び上気道感染等の感染症，下痢及び腹痛等の胃腸障害，発熱，注射部位反応，頭痛であった。重症度は軽度又は中等度の事象が多かった。ほとんどが処置なし，薬物治療等の処置により消失し，治験薬の投与中止や休薬を要することなく管理可能であった。

既存治療で効果不十分又は不耐容の crFMF，TRAPS，HIDS に対し，カナキヌマブを投与した場合の安全性プロファイルは，既承認の適応症に対する使用経験から特定された安全性プロファイルと同様であった。

以上の結果より，カナキヌマブの FMF，TRAPS，MKD/HIDS に対する有効性及び安全性が確認でき，これらの疾患を追加する一部変更承認申請を行うこととした。

4 特徴及び有用性

FMF，TRAPS，MKD/HIDS 患者の再燃を速やかに寛解させ，寛解が継続した。

- FMF，TRAPS，MKD/HIDS 患者で，投与開始後 15 日までに再燃の寛解が得られ，投与後 16 週までに再燃しなかった被験者の割合を主要評価項目として，プラセボ群に対するカナキヌマブ 150 mg 4 週間隔投与群の優越性が確認された。

患者の炎症マーカーの正常化，社会的 QOL の改善が期待される。

- FMF，TRAPS，MKD/HIDS は繰り返す発作の再燃とその治療に入院を要すること等により，患者の社会的 QOL を著しく損なっている。また，最悪の場合に死に至る重篤な疾患であるにもかかわらず，治療選択肢は極めて限られている。N2301 試験では，炎症マーカーの正常化，QOL の改善効果が示されており，カナキヌマブがこれらの疾患に対し有用な治療薬となることが期待される。

カナキヌマブの有効性は年齢，前治療の有無によらず認められた。

- FMF，TRAPS，MKD/HIDS に対して，現在国内で承認されている治療薬はない。また，TRAPS，MKD/HIDS に対しては，海外でも承認されている治療薬はなく，対症治療が行われている。
- N2301 試験で，カナキヌマブ投与の有効性は，年齢，コルヒチンの併用有無（crFMF 患者においてのみ評価），生物学的製剤による前治療の有無によらず認められ，これらの部分集団に対する効果に大きな違いはみられなかった。

カナキヌマブの効果は長期的に維持された。

- Proof of concept 試験（D2203 試験，D2402 試験，D2204 試験，DTR01 試験）において，カナキヌマブの効果は長期に維持され，効果の減弱は見られなかった。

TRAPS，MKD，FMF 患者での新たな安全性リスクは確認されなかった。

- N2301 試験における主な有害事象は，FMF，TRAPS，MKD/HIDS，に共通して鼻咽頭炎及び上気道感染等の感染症，下痢及び腹痛等の胃腸障害，発熱，注射部位反応，頭痛であった。重症度については，軽度又は中等度の事象が多く，ほとんどが処置なし，薬物治療等の処置により消失し，治験薬の投与中止や休薬を要することなく管理可能であった。
- FMF，TRAPS，MKD/HIDS 患者に対しカナキヌマブを投与した場合の特定された安全性プロファイル，は既承認の適応症の使用経験から特定された安全性プロファイルと同様であった。

5 まとめ

FMF，TRAPS，MKD/HIDS は，発作の再燃を繰り返し，その治療に入院を要する等，患者の社会的 QOL を著しく損なう疾患であるが，2016 年 4 月現在日本国内で承認された治療薬はない。N2301（国際共同第 III 相）試験において，カナキヌマブはこれらの疾患の発作の再燃を寛解し，患者の QOL を改善することが示された。

カナキヌマブは 2011 年 9 月の承認以降，国内 CAPS 患者における使用経験があり，今回実施された N2301 試験の結果，FMF，TRAPS，MKD/HIDS 患者における安全性プロファイルは CAPS 患者の安全性プロファイルと同様であった。FMF，TRAPS，MKD/HIDS 患者で見られた副作用とその重症度の程度は予測された範囲のものであり，多くは軽度で処置により消失し，管理可能であった。

以上より，カナキヌマブは FMF，TRAPS，MKD/HIDS 患者に対して有用な治療薬になり得ると考え，以下のとおり承認事項一部変更承認申請を行うこととした。

【申請品目】

イラリス皮下注用 150 mg

【効能又は効果（案）】（下線部が本一変申請追加箇所）

1. クリオピリン関連周期性症候群；家族性寒冷自己炎症症候群，マックル・ウェルズ症候群，新生児期発症多臓器系炎症性疾患
2. 家族性地中海熱
3. TNF 受容体関連周期性症候群
4. メバロン酸キナーゼ欠損症／高 IgD 症候群

【用法及び用量（案）】（下線部が本一変申請追加箇所）

1. クリオピリン関連周期性症候群

   通常，体重 40 kg 以下の患者にはカナキヌマブ（遺伝子組換え）として 1 回 2 mg/kg を，体重 40 kg を超える患者には 1 回 150 mg を 8 週毎に皮下投与する。

   十分な臨床的効果（皮疹及び炎症症状の寛解）がみられない場合には適宜漸増するが，1 回最高用量は体重 40 kg 以下の患者では 8 mg/kg，体重 40 kg を超える患者では 600 mg とする。

   最高用量まで増量し，8 週以内に再燃がみられた場合には，投与間隔を 4 週間まで短縮できる。

   なお，症状に応じて 1 回投与量の増減を検討すること。

2. 家族性地中海熱及び TNF 受容体関連周期性症候群

   通常，体重 40 kg 以下の患者にはカナキヌマブ（遺伝子組換え）として 1 回 2 mg/kg を，体重 40 kg を超える患者には 1 回 150 mg を，4 週毎に皮下投与する。

   十分な臨床効果がみられない場合には，投与後 7 日以降に，体重 40 kg 以下の患者には 1 回 2 mg/kg を，体重 40 kg を超える患者には 1 回 150 mg を，必要に応じて追加投与する。また，4 週毎の次回投与時より，1 回投与量をそれぞれ 4 mg/kg，300 mg に原則として増量する。

   なお，症状に応じて 1 回投与量の増減を検討するが，1 回最高用量は体重 40 kg 以下の患者では 4 mg/kg，体重 40 kg を超える患者では 300 mg を超えないこと。

3. メバロン酸キナーゼ欠損症／高 IgD 症候群

   通常，体重 40 kg 以下の患者にはカナキヌマブ（遺伝子組換え）として 1 回 2 mg/kg を，体重 40 kg を超える患者には 1 回 150 mg を，4 週毎に皮下投与する。

   十分な臨床効果がみられない場合には，投与後 7 日以降に，体重 40 kg 以下の患者には 1 回 2 mg/kg を，体重 40 kg を超える患者には 1 回 150 mg を，必要に応じて追加投与する。また，4 週毎の次回投与時より，1 回投与量をそれぞれ 4 mg/kg，300 mg に原則として増量する。

   増量後十分な臨床効果がみられない場合には，増量後 7 日以降に，体重 40 kg 以下の患者には 1 回 2 mg/kg を，体重 40 kg を超える患者には 1 回 150 mg を必要に応じて追加投与する。また，4 週毎の次回投与時より，1 回投与量をそれぞれ 6 mg/kg，450 mg に原則として増量する。

なお，症状に応じて 1 回投与量の増減を検討するが，1 回最高用量は体重 40 kg 以下の患者では 6 mg/kg，体重 40 kg を超える患者では 450 mg を超えないこと。

なお，FMF に対する治療薬としてコルヒチンが平成 28 年 9 月 28 日に承認された。コルヒチンの承認及び審査中の独立行政法人医薬品医療機器総合機構との協議内容を踏まえ，効能又は効果（案），及び用法及び用量（案）は以下の通り変更した。

【効能又は効果（案）】（下線部が本一変申請追加箇所）

1. 以下のクリオピリン関連周期性症候群
   - 家族性寒冷自己炎症症候群
   - マックル・ウェルズ症候群
   - 新生児期発症多臓器系炎症性疾患
2. 既存治療で効果不十分な家族性地中海熱
3. TNF 受容体関連周期性症候群
4. 高 IgD 症候群（メバロン酸キナーゼ欠損症）

【用法及び用量（案）】（下線部が本一変申請追加箇所）

1. クリオピリン関連周期性症候群

   通常，体重 40 kg 以下の患者にはカナキヌマブ（遺伝子組換え）として 1 回 2 mg/kg を，体重 40 kg を超える患者には 1 回 150 mg を 8 週毎に皮下投与する。

   十分な臨床的効果（皮疹及び炎症症状の寛解）がみられない場合には適宜漸増するが，1 回最高用量は体重 40 kg 以下の患者では 8 mg/kg，体重 40 kg を超える患者では 600 mg とする。

   最高用量まで増量し，8 週以内に再燃がみられた場合には，投与間隔を 4 週間まで短縮できる。

   なお，症状に応じて 1 回投与量の増減を検討すること。
2. 家族性地中海熱及び TNF 受容体関連周期性症候群

   通常，体重 40 kg 以下の患者にはカナキヌマブ（遺伝子組換え）として 1 回 2 mg/kg を，体重 40 kg を超える患者には 1 回 150 mg を，4 週毎に皮下投与する。

   十分な臨床的効果がみられない場合には追加投与又は適宜漸増するが，1 回最高用量は体重 40 kg 以下の患者では 4 mg/kg，体重 40 kg を超える患者では 300 mg とする。
3. 高 IgD 症候群（メバロン酸キナーゼ欠損症）

   通常，体重 40 kg 以下の患者にはカナキヌマブ（遺伝子組換え）として 1 回 2 mg/kg を，体重 40 kg を超える患者には 1 回 150 mg を，4 週毎に皮下投与する。

   十分な臨床的効果がみられない場合には追加投与又は適宜漸増するが，1 回最高用量は体重 40 kg 以下の患者では 6 mg/kg，体重 40 kg を超える患者では 450 mg とする。

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1.6 外国における使用状況等に関する資料

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1 外国における使用状況等

2016 年 9 月現在，本剤は米国，EU 等世界 70 カ国以上で承認されている。主要国での承認状況を，Table 1-1 に示す。

Table 1-1 主要国での承認状況

国名	販売名	承認年月日	剤型・含量	効能・効果
米国	ILARIS	2009 年 6 月 17 日	凍結乾燥注射剤・溶解後の 1 mL 溶液中にカナキヌマブ 150 mg を含有	クリオピリン関連周期性症候群（家族性寒冷自己炎症症候群，マックル・ウェルズ症候群），全身型若年性特発性関節炎，TNF 受容体関連周期性症候群，高 IgD 症候群／メバロン酸キナーゼ欠損症，家族性地中海熱
EU	Ilaris	2009 年 10 月 23 日	凍結乾燥注射剤・溶解後の 1 mL 溶液中にカナキヌマブ 150 mg を含有	クリオピリン関連周期性症候群（家族性寒冷自己炎症症候群，マックル・ウェルズ症候群，新生児期発症多臓器系炎症性疾患），スティル病，痛風性関節炎

2 外国の添付文書等の概要

米国の添付文書（2016 年 9 月改訂）の概略を Table 2-1 に，EU 共通の添付文書（2016 年 8 月改訂）を Table 2-2 に示す。

Table 2-1 米国の添付文書の概略

販売名	イラリス皮下注用
剤型・含量	イラリスは 180 mg の白色の皮下注用凍結乾燥製剤として提供される。本剤を皮下投与する前に，1 mL の防腐剤を含まない滅菌注射用水で溶解する。溶解後の容量は 1.2 mL となる。溶解後のイラリスには目視可能な粒子は含まれておらず，澄明から乳白色にわずかに混濁した，無色からごくわずかに黄褐色を帯びた 150 mg/mL 溶液となる。
効能・効果	**クリオピリン関連周期性症候群（CAPS）** イラリス（カナキヌマブ）は，成人及び 4 歳以上の小児における以下のクリオピリン関連周期性症候群（CAPS）の治療を適応とするインターロイキン（IL）-1β 阻害剤である。 ● 家族性寒冷自己炎症症候群（FCAS） ● マックル・ウェルズ症候群（MWS） **TNF 受容体関連周期性症候群（TRAPS）** イラリスは，成人及び小児における TNF 受容体関連周期性症候群（TRAPS）の治療を適応症とする治療薬である。 **高 IgD 症候群（HIDS）／メバロン酸キナーゼ欠損症（MKD）** イラリスは，成人及び小児における高 IgD 症候群（HIDS）／メバロン酸キナーゼ欠損症（MKD）の治療を適応症とする治療薬である。 **家族性地中海熱（FMF）** イラリスは，成人及び小児における家族性地中海熱（FMF）の治療を適応症とする治療薬である。 **全身型若年性特発性関節炎（SJIA）**

販売名	イラリス皮下注用
	イラリスは，2 歳以上の患者における活動性全身型若年性特発性関節炎（SJIA）を適応症とする治療薬である。
用法・用量	**<u>投与に関する基本情報</u>** 皮下注による投与のみ。 **クリオピリン関連周期性症候群（CAPS）** 体重が 40 kg を超える CAPS 患者に対するイラリスの推奨用量は 150 mg である。体重 15 kg 以上 40 kg 以下の CAPS 患者に対する推奨用量は 2 mg/kg である。体重 15～40 kg で十分な効果がみられない小児には，投与量を 3 mg/kg に増量できる。 イラリスは 8 週ごとに単回皮下投与する。 **TNF 受容体関連周期性症候群（TRAPS），高 IgD 症候群（HIDS）／メバロン酸キナーゼ欠損症（MKD），家族性地中海熱（FMF）** TRAPS，HIDS/MKD 及び FMF 患者に対するイラリスの推奨用量は体重を基準に算出する。 体重 40 kg 以下の患者に対する推奨用量は 2 mg/kg を 4 週毎に投与する。臨床的に十分な効果が見られない場合には，4 mg/kg 4 週間隔投与に増量できる。 体重 40 kg を超える患者に対する推奨用量は 150 mg を 4 週毎に投与する。臨床的に十分な効果が見られない場合には，300 mg 4 週間隔投与に増量できる。 **全身型若年性特発性関節炎（SJIA）** 体重 7.5 kg 以上の SJIA 患者に対するイラリスの推奨用量は 4 mg/kg であり（最高 300 mg），4 週ごとに皮下投与する。 **4 ステップの調製及び投与方法** **ステップ 1：**無菌的手技により，18 ゲージ×2"の注射針を装着した 1 mL の注射筒を用いて，防腐剤無添加の無菌注射用水 1 mL をイラリスのバイアルにゆっくりと注入して溶解する。 **ステップ 2：**約 45 度の角度でバイアルを約 1 分間ゆっくりと回転させた後，5 分間静置する。バイアルを振らないこと。バイアルをゆっくりと 10 回上下反転させる。指でゴム栓に触れないようにする。 **ステップ 3：**室温で約 15 分間静置して澄明な液にする。調製した溶液の最終濃度は 150 mg/mL である。バイアルを振らないこと。溶液中に粒状物質がある場合は使用しないこと。バイアルの側面を軽く叩き，ゴム栓に付着している液体を下に移動させる。調整した溶液には実質的に粒子は含まれておらず，澄明からわずかに乳白色に混濁している。溶液は無色であるが，ごくわずかに黄褐色のこともある。溶液が明らかに褐変している場合には使用しないこと。溶解後 60 分以内に使用する場合は，明るい場所を避け，室温で保管することが可能である。溶解後 60 分以内に使用しない場合は，溶液を冷蔵庫内（2°C～8°C 又は 36°F～46°F）で保管し，4 時間以内に使用すること。本剤溶解時に軽く泡立つことがあるが，問題はない。 **ステップ 4：**投与量に応じて必要な液量（0.2 mL～1 mL）を無菌の注射筒と注射針を用いて注意深く採取し，27 ゲージ×0.5"の注射針を用いて皮下投与する。 イラリスの曝露量が不足することがあるため，瘢痕組織への投与は避けること。 イラリス 180 mg 注射用粉末は，1 回使い切り型のバイアルに充填されている。余った溶液や廃棄物は，各地域の要件に従って廃棄すること。
使用上の注意	**<u>禁忌</u>** 本剤の有効成分又はその他の添加物に対し過敏症の既往歴のある患者［*「「警告及び使用上の注意」及び「副作用」の項参照」*］。 **<u>警告及び使用上の注意</u>** **重篤な感染症**

販売名	イラリス皮下注用
	イラリスは，重篤な感染症発現のリスク増大と関連性がある。医師は，感染症のある患者，再発性感染症の既往歴のある患者，又は易感染性の状態にある患者にイラリスを投与する場合は十分注意すること。医療介入の必要な活動性感染症の患者にはイラリスを投与しないこと。患者に重篤な感染症が発現した場合は，イラリスの投与を中止すること。 イラリスを投与した患者に主に上気道感染等の感染症が報告されており，重篤な感染症も報告されている。報告された感染症は，概ね標準治療が奏効した。例外的なケースとして，イラリスの投与中に異常な感染症や日和見感染（例：アスペルギルス症，非定型マイコバクテリア感染症，サイトメガロウイルス，帯状疱疹）の発現が報告されている。イラリスとこれらの事象との因果関係は除外できない。臨床試験では，イラリスと腫瘍壊死因子（TNF）阻害剤の併用投与は行っていない。別の IL-1 阻害剤と TNF 阻害剤の併用により，重篤な感染症の発現頻度が増加することが報告されている。重篤な感染症発現のリスクが増大することがあるため，イラリスと TNF 阻害剤は併用しないことが望ましい*［「薬物相互作用」の項参照］*。 TNF を阻害することにより免疫系に作用する薬剤は，結核の新規発症や潜在性結核症の再燃のリスク増大と関連性がある。イラリス等の IL-1 阻害剤の投与により，結核の再燃や日和見感染の発現リスクが増大する可能性がある。 イラリスを含む免疫療法を開始する前に，活動性結核及び潜在性結核に関して患者の評価を行うこと。すべての患者に適切なスクリーニング検査を実施すること。イラリスは結核陽性患者において試験は行っておらず，潜在性結核患者に対するイラリスの安全性は不明である。結核陽性反応の患者は，イラリスによる治療を開始する前に標準治療に従って治療すること。すべての患者に対し，イラリス投与中又は投与後に結核を示唆する徴候又は症状（例：持続する咳，体重減少，微熱）が発現した場合や，結核に曝露したリスクが高い場合は，医師の診察を受けるよう指導すること。 医療提供者は，イラリスによる治療開始前に，現行の CDC ガイドラインに従って潜在性結核が疑われる患者の評価及び治療を行うこと。 **免疫抑制** 抗インターロイキン-1（IL-1）療法が悪性腫瘍の発現に及ぼす影響については不明である。しかし，イラリスを含む免疫抑制剤の投与により，悪性腫瘍発現のリスクが増大することがある。 **過敏症** イラリスの投与に対する過敏症反応が報告されている。臨床試験では，アナフィラキシー反応は報告されていない。治療中の基礎疾患の症状が過敏症の症状に似ている場合もあることを認識しておくこと。イラリスに対し過敏症の臨床症状の既往歴がある患者にはイラリスを投与しないこと*［「禁忌」及び「副作用」の項参照］*。 **ワクチン接種** イラリス投与中は生ワクチン接種を行わないこと*［「薬物相互作用」の項参照］*。イラリス投与中の患者における生ワクチン接種による有効性又は二次感染のリスクに関するデータは得られていないため，本剤投与中は生ワクチン接種を行わないこと。また，イラリスは新たな抗原に対する正常な免疫応答を妨げることがあるため，イラリス投与中の患者にはワクチン接種が有効でない可能性がある。イラリス投与中の患者における不活化（死菌）抗原のワクチン接種に対するデータは限られている*［「薬物相互作用」の項参照］*。 IL-1 阻害薬は感染に対する免疫応答を妨げることがあるため，成人及び小児患者はイラリスの投与開始前に，必要に応じて推奨されるすべてのワクチン（肺炎球菌ワクチン及びインフルエンザ不活化ワクチンを含む）を可能な限り接種しておくことが望ましい（現在推奨されているワクチン接種スケジュールについては，疾病対策センターのウェブサイト http://www.cdc.gov/vaccines/schedules/index.html を参照のこと）。 **マクロファージ活性化症候群**

販売名	イラリス皮下注用

マクロファージ活性化症候群（MAS）は，リウマチ性疾患，特に SJIA 患者に発現することのある生命を脅かす障害として知られており，積極的な治療を行う必要がある。感染症や SJIA は MAS を誘発することが判明しているため，医師は感染症の症状や SJIA の増悪に注意すること。臨床試験でカナキヌマブを投与した 201 例の SJIA 患者のうち，MAS の発現が 11 件報告された。臨床試験での経験では，SJIA 患者にイラリスを投与しても MAS の発現率は増加しないと考えられるが，最終的な結論には至っていない。

副作用

CAPS，TRAPS，HIDS/MKD，FMF 又は SJIA の介入試験において，約 350 例の小児（17 歳以下）を含む 570 例の患者にイラリスを投与した。最も報告の多かった副作用は感染症で，主に上気道感染であった。重篤な感染症の発現もみられたが，事象の大半は軽度から中等度であった。

イラリスを投与した患者において，日和見感染の発現も報告されている*［「警告及び使用上の注意」の項参照］*。

臨床試験における経験

臨床試験はさまざまに異なる条件下で実施しているため，ある薬物の臨床試験で認められた副作用の発現頻度を他の薬物の臨床試験で認められた発現頻度と直接比較することはできないほか，臨床試験で認められた副作用の発現頻度は，使用実態下での副作用の発現頻度を反映していないこともある。

CAPS の治療

本項に記載のデータは，FCAS の 20 例，MWS の 72 例，MWS/NOMID（新生児期発症多臓器系炎症性疾患）の併発例 10 例，非 FCAS 非 MWS の 1 例，及び誤診の 1 例を含む 104 例の成人及び小児 CAPS 患者を対象としたプラセボ対照試験（35 例）及び非対照試験におけるイラリスへの曝露状況を反映したものである。62 例の患者がイラリスに 6 ヵ月以上曝露し，56 例は 1 年以上，4 例は 3 年以上曝露した。CAPS 患者では，計 9 件の重篤な副作用が報告された。これらの副作用の中には，回転性めまい（2 例）と，虫垂切除後の腹腔内膿瘍（1 例）を含む感染症（3 例）もあった。CAPS 患者において最も報告の多かった（10%以上）イラリスの投与に関連のある副作用は，鼻咽頭炎，下痢，インフルエンザ，鼻炎，回転性めまい，頭痛，気管支炎，胃腸炎，咽頭炎，体重増加，筋骨格痛及び悪心であった。1 例の患者は感染症が疑われたため投与を中止した。

CAPS 試験 1 では，8 週間の非盲検期（パート 1），その後の 24 週間の無作為化投与中止期（パート 2），その後の 16 週間の非盲検期（パート 3）においてイラリスの安全性を検討した。すべての患者にイラリス 150 mg あるいは体重 15 kg 以上 40 kg 以下の場合は 2 mg/kg を皮下投与した（表 1 を参照）。

パート 1 ではすべての CAPS 患者にイラリスを投与したため，有害事象（AE）に関する対照のデータはない。表 1 のデータは，カナキヌマブを投与した全 CAPS 患者に発現したすべての AE である。CAPS 試験 1 では，3 つの試験期間を通して，有害事象の種類又は頻度に関する規則性は認められなかった。

表 1　CAPS 患者を対象とした第 3 相試験のパート 1 から 3 において 10%を超えた有害事象を基本語別にみた例数（%）

基本語	イラリス N=35 n（%）
有害事象が発現した患者数（%）	35 (100)
鼻咽頭炎	12 (34)
下痢	7 (20)
インフルエンザ	6 (17)
鼻炎	6 (17)
悪心	5 (14)
頭痛	5 (14)

販売名	イラリス皮下注用

気管支炎	4 (11)
胃腸炎	4 (11)
咽頭炎	4 (11)
体重増加	4 (11)
筋骨格痛	4 (11)
回転性めまい	4 (11)

回転性めまい

CAPS 試験の患者の 9～14%（MWS 患者のみ）において回転性めまいの発現が報告されており，重篤な有害事象が 2 例報告された。いずれの事象もイラリスの投与を中断することなく消失した。

注射部位反応

CAPS 試験 1 における皮下注射部位反応は，パート 1 で軽度反応が 9%の患者に，パート 2 で軽度又は中等度の反応が各 1 例（7%）に，パート 3 で軽度の局所反応が 1 例にみられた。重度の注射部位反応は報告されなかったほか，投与中止に至った反応もなかった。

TRAPS, HIDS/MKD, FMF の治療

TRAPS, HIDS/MKD, FMF を対象とした第Ⅲ相臨床試験（試験 1）では，12 週間のスクリーニング期（パート 1），16 週間のプラセボとの比較でイラリスの有効性を確認する二重盲検期（パート 2），24 週間の再ランダム化投与中断・投与頻度低減期（パート 3），72 週間の非盲検期（パート 4）でイラリスの 3 つのコホート（TRAPS，HIDS/MKD，FMF）に対する安全性を検証した。パート 2 でイラリス群に割り付けられた患者は体重が 40 kg を超えている場合，150 mg 4 週間隔で皮下投与された。（体重が 40 kg 以下の場合は 2 mg/kg 投与された。）

TRAPS, HIDS/MKD, FMF を対象とした試験 1 のパート 2 では，90 名がイラリス群に割り付けられ，91 名がプラセボ群に割り付けられた。イラリス群に割り付けられた患者のうち，55.6%は 16 週間初回用量で維持され，6.7%を Day 7 から Day 15 の間にイラリスの追加投与がされた。プラセボ群に割り付けられた患者のうち，9.9%は 16 週間プラセボが維持され，28.6%は Day 15 までにイラリス群に切り替わった。

全体を通して，47.61 patient-years の累積的なカナキヌマブの曝露に TRAPS 患者 43 名，HIDS/MKD 患者 68 名，FMF 患者 58 名が安全性セットに含まれた。プラセボ群の累積的な曝露は 8.03 patient-years であった。

TRAPS, HIDS/MKD, FMF を対象とした試験 1 のパート 2 で，3 から 76 歳の TRAPS 患者 22 名，2 から 43 歳 HIDS/MKD 患者 37 名，2 から 60 歳の FMF 患者 31 名は，プラセボとの比較試験の中で初回イラリス 150 mg 4 週間隔投与群に割り付けられた。さらに，4 名の非割り付け患者（20 から 29 歳の non-exon10 を保有する FMF 患者 2 名と 1 歳の HIDS/MKD 患者 2 名）はパート 2 においてオープンラベル治療がされた。

TRAPS, HIDS/MKD, FMF 患者でイラリスの治療によって最も高頻度（10%以上）に報告された副作用は投与部位反応と鼻咽頭炎であった。TRAPS, HIDS/MKD, FMF 患者でイラリスの治療によって報告された副作用（3%以上）は，注射部位反応（10.1%），鼻咽頭炎を含む感染症（10.7%），上気道感染（7.1%），鼻炎（5.3%），胃腸炎（3.0%），及び咽頭炎（3.0%）であった。重篤な感染症（結膜炎，肺炎，咽頭炎，咽頭扁桃炎など）は TRAPS, HIDS/MKD, FMF を対象とした試験 1 のパート 2 で約 2.4%（100 人･日あたり 0.03）見られた。

イラリス投与群では，1 名の TRAPS 患者及び 2 名の HIDS/MKD 患者が有害事象で投与中止した。有害事象で投与中止した FMF 患者はいなかった。

注射部位反応

TRAPS, HIDS/MKD, FMF を対象とした試験 1 のパート 2 では皮下注射部位反応が 10.1%の患者で見られたが，いずれも軽度または中等度で忍容であった。重度及び治療を中止する注射部位反応は報告されていない。

販売名	イラリス皮下注用

SJIA の治療

臨床試験では，2 歳以上 20 歳未満の SJIA 患者合計 201 例にイラリスを投与した。2 つの第 III 相臨床試験において，イラリスの安全性をプラセボと比較検討した*［「臨床試験」の項参照］*。SJIA 試験 1 の患者にはイラリス 4 mg/kg（43 例）又はプラセボ（41 例）を単回皮下投与し，15 日目に有効性の評価項目を評価し，29 日目までの安全性解析を行った。SJIA 試験 2 は，非盲検単群実薬投与期（パート I）及び，その後の無作為化二重盲検プラセボ対照 event-driven 中止デザイン（パート II）の 2 つのパートで構成される試験であった。全体で 177 例の患者を本試験に登録した後，パート I ではイラリス 4 mg/kg（最高 300 mg）を投与し，パート II では 100 例の患者にイラリス 4 mg/kg（最高 300 mg）を 4 週ごとに投与するかプラセボを投与した。両試験において，プラセボ群よりも発現率が高かった副作用（10%以上）を表 2 に示す。SJIA 患者においてイラリスの投与と関連のあった副作用は，感染症，腹痛及び注射部位反応であった。両試験のイラリス投与患者の約 4～5%（100 人・日あたり 0.02～0.17）に，重篤な感染症（例：肺炎，水痘，胃腸炎，麻疹，敗血症，中耳炎，副鼻腔炎，アデノウイルス感染，リンパ節膿瘍，咽頭炎）が観察された。

副作用は MedDRA 第 15.0 版の器官別大分類に従って記載している。

表 2　　SJIA の主要試験における副作用の要約一覧

	SJIA 試験 2			SJIA 試験 1	
	パート I	パート II			
	イラリス 177 例 n (%) (IR)^	イラリス 50 例 n (%) (IR)	プラセボ 50 例 n (%) (IR)	イラリス 43 例 n (%) (IR)	プラセボ 41 例 n (%) (IR)
感染症および寄生虫症					
すべての感染症（例：鼻咽頭炎、（ウイルス性）上気道感染、肺炎、鼻炎、咽頭炎、扁桃炎、副鼻腔炎、尿路感染、胃腸炎、ウイルス感染）	97 (54.8%) (0.91)	27 (54%) (0.59)	19 (38%) (0.63)	13 (30.2%) (1.26)	5 (12.2%) (1.37)
胃腸障害					
腹痛（上腹部）	25 (14.1%) (0.16)	8 (16%) (0.15)	6 (12%) (0.08)	3 (7%) (0.25)	1 (2.4%) (0.23)
皮膚および皮下組織障害					
注射部位反応*					
軽度	19 (10.7%)	6 (12.0%)	2 (4.0%)	0	3 (7.3%)
中等度	2 (1.1%)	1 (2.0%)	0	0	0

n= 患者数

^ IR=曝露量で補正した 100 人・日あたりの発現率

* 試験中止に至った注射部位反応はなかった。

過敏症

臨床試験では，アナフィラキシー反応の報告はなかった。CAPS 試験では 1 例の患者が投与を中止したが，TRAPS, HIDS/MKD, FMF，SJIA を対象とした試験では過敏症反応のため投与を中止した患者はいなかった。イラリスに対し過敏症の臨床症状の既往歴がある患者にはイラリスを投与しないこと*［「禁忌」及び「警告及び使用上の注意」の項参照］*。

免疫原性

販売名	イラリス皮下注用
	バイオセンサー結合アッセイ又はブリッジング免疫測定法を用いて，イラリスを投与した患者におけるカナキヌマブに対する抗体を検出した。イラリス抗体は，CAPS 及び SJIA の治療のためイラリスを投与した患者のそれぞれ約 1.5%及び 3.1%で認められた。中和抗体は検出されなかった。抗体の発生と臨床反応又は有害事象との間に明らかな相関は認められなかった。CAPS の臨床試験ではバイオセンサー結合アッセイを使用し，SJIA の臨床試験の大半ではブリッジングアッセイを使用した。アッセイで得られるデータは，アッセイの感度と特異度，アッセイの方法，試料の取扱い，試料採取のタイミング，併用薬，基礎疾患及び検証した患者数を含むいくつかの因子に強く依存する。このため，CAPS と SJIA の臨床試験の間でカナキヌマブ抗体の発現率を比較したり，抗体の発現率を他の薬剤と比較すると，誤解を招くことおそれがある。 150 mg 及び 300 mg で 16 週間イラリスで治療された TRAPS, HIDS/MKD, FMF 患者では抗カナキヌマブ抗体の発現陽性は見られなかった。 **臨床検査値** ***血液*** TRAPS, HIDS/MKD, FMF TRAPS, HIDS/MKD, FMF を対象とした試験 1 において，好中球数減少（≧Grade 2）が 6.5%の患者で報告され，血小板数減少（≧Grade 2）が 0.6%の患者で報告された。 SJIA イラリスの臨床試験では，白血球，好中球及び血小板の平均値が減少した。 SJIA 試験 2 の無作為化プラセボ対照パートにおいて正常値下限（LLN）の 0.8 倍以下の白血球数（WBC）減少が報告された患者は，イラリス群が 5 例（10.4%）であったのに対し，プラセボ群は 2 例（4.0%）であった。1×10^9/L 未満の一過性の好中球絶対数（ANC）減少が報告された患者は，イラリス群が 3 例（6.0%）であったのに対し，プラセボ群は 1 例（2.0%）であった。0.5×10^9/L 未満の ANC がイラリス群の 1 例で観察されたが，プラセボ群ではこのような患者はいなかった。 イラリスを投与した患者 3 例（6.3%）とプラセボを投与した患者 1 例（2.0%）において，軽度（LLN 未満かつ 75×10^9/L を超える）及び一過性の血小板数減少が観察された。 ***肝トランスアミナーゼ*** イラリスを投与した患者において，トランスアミナーゼ上昇が報告されている。 SJIA 試験 2 の無作為化プラセボ対照パートでは，イラリスを投与した患者 2 例（4.1%）とプラセボを投与した患者 1 例（2.0%）において，正常値上限（ULN）の 3 倍以上の ALT 増加及び／又は AST 増加が報告された。いずれの患者も，次の来院時には正常値であった。 ***ビリルビン*** イラリスを投与した患者において，トランスアミナーゼ上昇を伴わない，無症候性で軽度の血清ビリルビン上昇が報告されている。 **薬物相互作用** イラリスと他の薬剤との相互作用を検討した正式な試験は実施されていない。 **TNF 阻害剤と IL-1 阻害剤** 他の患者集団では，他の IL-1 阻害剤と TNF 阻害剤の併用投与により，重篤な感染症の発現頻度が増加し，好中球減少症のリスク増大が認められている。イラリスと TNF 阻害剤の併用でも同様の毒性が発現する可能性があり，重篤な感染症発現のリスクが増大するおそれがあるため，併用しないことが望ましい。*［「警告及び使用上の注意」の項参照］*。 イラリスと他の IL-1 阻害薬の併用投与については検討していない。イラリスと遺伝子組換え IL-1 ra との間に薬理学的相互作用が生じる可能性があるため，イラリスと IL-1 又はその受容体を阻害する他剤との併用は行わないことが望ましい。 **ワクチン接種**

販売名	イラリス皮下注用
	イラリス投与中の患者における生ワクチン接種による影響，又は生ワクチン接種による二次感染に関するデータは得られていない。したがって，本剤投与中は生ワクチンの接種を行わないこと。小児及び成人患者は，可能であれば，本剤の投与開始前に，最新のワクチン接種ガイドラインに従ってすべてのワクチンを接種しておくことが望ましい*［「警告及び使用上の注意」の項参照］*。 **チトクローム P450 の基質** CYP450 の発現は慢性炎症の過程に生じるサイトカイン（例：IL-1）レベルの上昇によって抑制される。したがって，IL-1 に結合するカナキヌマブ等の分子は，CYP450 酵素の形成を正常化する可能性があると考えられる。治療域が狭く CYP450 基質が代謝に関連する薬剤（例：ワルファリン）において，投与量を個別に調節することは臨床的に意義がある。このような種類の薬剤を投与している患者にカナキヌマブの投与を開始する場合は，これらの薬剤の効果や薬物濃度に関するモニタリングを行い，必要に応じて，薬剤の投与量を患者ごとに調節する必要がある。 **特別な集団における使用** **妊婦** **リスクの概要** 市販後の妊婦に対するイラリスの使用の報告は本剤によるリスクを報告するにはデータが限られており，不十分である。カナキヌマブのようなモノクローナル抗体は妊娠の進捗によって胎盤内を線形に透過する。そのため，考えられる胎児への曝露は，妊娠中期及び後期の方が高い。マーモセットによる胚胎児発生に関する試験でカナキヌマブをヒト最大推奨用量（MRHD）の 11 倍以上（血漿中濃度-時間曲線下面積［AUC］の比較による）を器官形成期以降に皮下投与した結果，胎児毒性や胎児奇形の根拠は認められなかった。マーモセットに MRHD の 11 倍以上のイラリスを胎児期に曝露した結果，胎児に骨格形成遅延が認められた。マウスの相同抗体を器官形成期に投与したマウスにおいても，同様の胎児の骨格形成遅延が認められた。骨格形成遅延は通常の骨格や骨とは別に予想される骨化状態からの変化である。これらの事象は通常可逆性または一時的なものであり出生後の生存に害を及ぼすものではない*［「動物データ」の項参照］*。 対象患者への予想される主要な先天性異常及び流産のリスク背景は不明である。一般の米国人において，臨床的に妊娠が認められた後予想される主要な先天性異常及び流産のリスク背景はそれぞれ 2 から 4%及び 15 から 20%である。 **データ** **動物データ** 胚胎児発生に関する試験において，妊娠マーモセットの妊娠 25～140 日目に，カナキヌマブを血漿 AUC での MRHD の約 11 倍以上（母体に 15，50 又は 150 mg/kg を週 2 回皮下投与）を曝露した。イラリスが胎児毒性又は胎児奇形を誘引するエビデンスは認められなかった。マーモセットにおいて骨格形成遅延が示唆される同時対照群と比較して，いずれの用量でも胎児における椎骨末端の骨化不全及び椎骨の不整列又は二分の発現頻度増加が認められた。カナキヌマブはマウス又はラットの IL-1 と交差反応しないため，妊娠マウスにマウスの相同抗体 15，50 又は 150 mg/kg を器官形成期の妊娠 6 日目，11 日目及び 17 日目に皮下投与した。胎児における頭頂骨及び前頭骨の骨化不全の発現率は，検討したいずれの用量でも用量依存的に増加した。 **授乳** **リスクの概要** カナキヌマブがヒトの母乳中に移行するかどうか，母乳を授乳した乳児への影響，または母乳生産への影響は不明である。ヒト IgG はヒトの母乳中に存在することが知られている。カナキヌマブの母乳への影響及び母乳を授乳した乳児への全身曝露の可能性は不明である。授乳による健康への影響は，母親のイラリスの臨床的必要性及び，授乳した乳児のカナキヌマブや母親の状態からの副作用の可能性を考慮すること。 **小児等への投与**

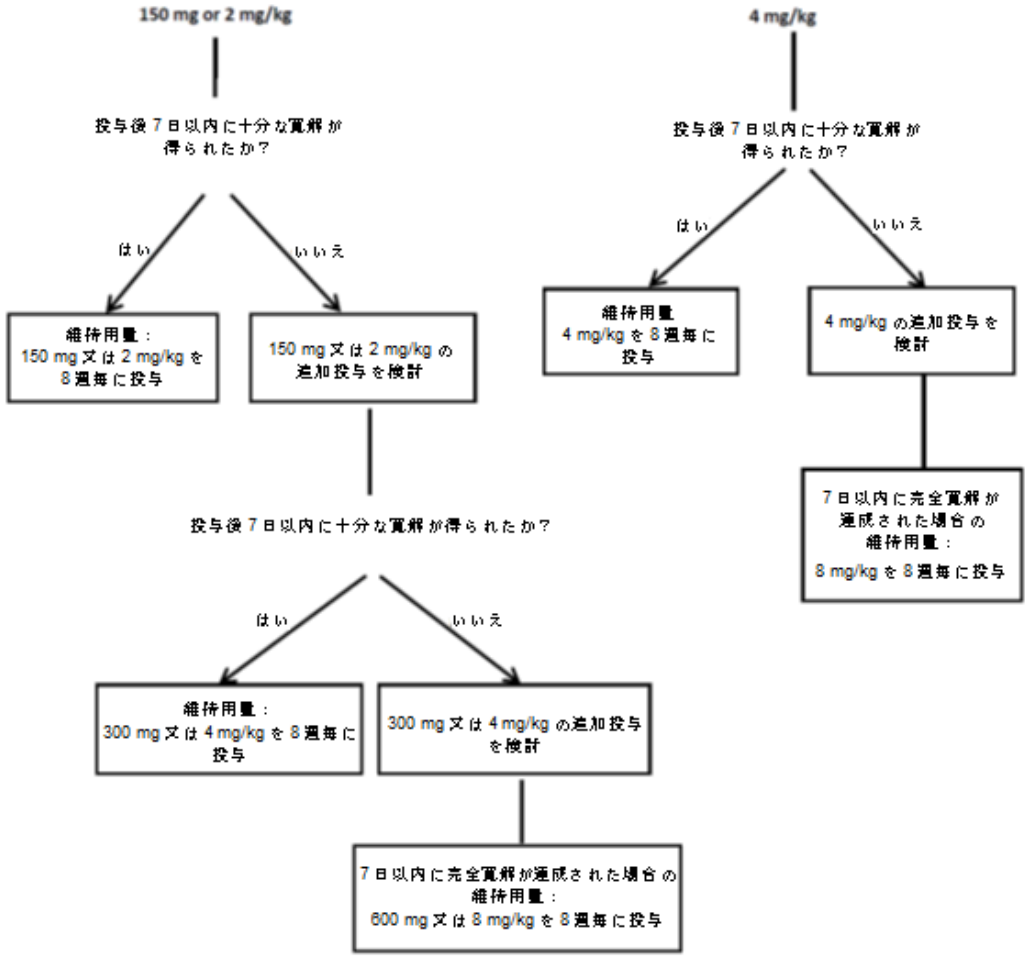
販売名	イラリス皮下注用
	イラリスの CAPS 試験には，4～17 歳の小児患者を合計で 23 例登録した（11 例は青年期の患者で，150 mg を皮下投与し，体重 15 kg 以上 40 kg 以下の 12 例の小児の患者には 2 mg/kg を投与した）。多数の患者では，臨床症状及び客観的な炎症マーカー（例：血清アミロイド A 及び C-反応性で改善が認められた。総合的に，小児及び成人患者におけるイラリスの安全性及び有効性は同等であった。最も高頻度に報告された感染症は上気道感染であった。4 歳未満の CAPS 患者に対するイラリスの安全性及び有効性は確立していない。*［「薬物動態」の項参照］*。 2 歳未満の SJIA 患者におけるイラリスの安全性及び有効性は確立していない*［「薬物動態」の項参照］*。 TRAPS, HIDS/MKD, FMF を対象とした試験では 3 疾患合計 102 名の小児患者（2 歳から 17 歳）がイラリスの投与を受けた。全体的に，イラリスの有効性，安全性，忍容性に臨床的意義のある相違は TRAPS, HIDS/MKD, FMF の患者全体（成人と小児の患者の合計，N=169）と比較して見られなかった。多くの小児患者は臨床的寛解が得られ，炎症マーカーの改善が見られた。 **高齢者への投与** イラリスの臨床試験に登録された 65 歳以上の被験者数では，若年被験者と反応性の違いについて検討することはできなかった。 **腎機能障害を有する患者** 腎機能障害を有する患者にイラリスを皮下投与した場合の薬物動態を正式に検討した試験は実施していない。 **肝機能障害を有する患者** 肝機能障害を有する患者にイラリスを皮下投与した場合の薬物動態を正式に検討した試験は実施していない。 **過量投与** 過量投与例は報告されていない。過量投与がされた場合は，副作用や有害作用の徴候及び症状を観察し，直ちに適切な処置を開始することが望ましい。
改訂年月日	2016 年 9 月 23 日

Table 2-2 EU 共通の添付文書の概略

販売名	イラリス 150 mg 凍結乾燥注射剤
剤型・含量	**【成分及び含量】** バイアル 1 本に 150 mg のカナキヌマブ*が含まれる。 溶解後の 1 mL 溶液中にカナキヌマブ 150 mg を含有する。 *カナキヌマブは，マウスハイブリドーマ Sp2/0 細胞に産生させた遺伝子組換えヒト型抗ヒトモノクローナル抗体である。 **【剤形】** 凍結乾燥注射剤 本粉末は白色である。
効能・効果	**クリオピリン関連周期性症候群** イラリスは，体重 7.5 kg 以上の成人，青年及び 2 歳以上の小児における以下のクリオピリン関連周期性症候群（CAPS）を適応症とする治療薬である。 ● マックル・ウェルズ症候群（MWS） ● 新生児期発症多臓器系炎症性疾患（NOMID）／慢性乳児期発症神経皮膚関節症候群（CINCA） ● 家族性寒冷自己炎症症候群（FCAS）／寒冷蕁麻疹様発疹以外の徴候及び症状も有する家族性寒冷蕁麻疹（FCU）

販売名	イラリス 150 mg 凍結乾燥注射剤
	<u>スティル病</u> イラリスは，成人発症型スティル病（AOSD）を含む活性型スティル病及び 2 歳以上で前治療の非ステロイド系抗炎症薬（NSAIDs）及び全身性コルチコステロイドにより十分な効果がみられなかった患者における活動性全身型若年性特発性関節炎（SJIA）を適応症とする治療薬である。イラリスは，単剤療法又はメトトレキサートとの併用療法として投与可能である。 **<u>痛風性関節炎</u>** イラリスは，頻繁な痛風性関節炎の発作（過去 12 ヵ月で少なくとも 3 回）のある成人患者で，非ステロイド系抗炎症薬（NSAIDs）及びコルヒチンが禁忌か，不耐性又は十分な効果がみられない患者，及びコルチコステロイドの継続投与が適切ではない患者の対症療法を適応とする。
用法・用量	CAPS 及びスティル病患者には，関連適応症の診断及び治療経験を有する専門医の監督下で投与を開始すること。 痛風性関節炎患者には，生物学的製剤の投与経験のある医師がイラリスを投与すること。 正しい投与手技について適切なトレーニングを受けた患者又はその介護者は，医師が適切と判断し，必要に応じて医学的フォローアップを受ける場合は，イラリスを投与してもよい。 **<u>CAPS</u>** **成人，青年及び 2 歳以上の小児** CAPS 患者に対するイラリスの推奨開始用量は以下のとおりである。 *<u>成人，青年及び 4 歳以上の小児：</u>* － 体重が 40 kg を超える患者には 150 mg － 体重 15 kg 以上 40 kg 以下の患者には 2 mg/kg － 体重 7.5 kg 以上 15 kg 未満の患者には 4 mg/kg *<u>2 歳以上 4 歳未満の小児：</u>* － 体重 7.5 kg 以上の患者には 4 mg/kg 本剤は 8 週ごとに単回皮下投与する。 開始用量が 150 mg 又は 2 mg/kg の患者については，投与開始後 7 日までに十分な臨床的効果（発疹及びその他の全身性の炎症症状の寛解）がみられない場合，イラリス 150 mg 又は 2 mg/kg の 2 回目の追加投与を検討できる。その後，完全寛解がみられた場合は，維持用量の 300 mg 又は 4 mg/kg を 8 週ごとに投与すること。この増量後 7 日までに十分な臨床的効果がみられない場合には，イラリス 300 mg 又は 4 mg/kg の 3 回目の追加投与を検討できる。その後，完全寛解が達成された場合は，個々の臨床的判断を基に維持用量の 600 mg 又は 8 mg/kg の 8 週ごと投与を検討すること。 開始用量が 4 mg/kg の患者については，投与開始後 7 日までに十分な臨床的効果がみられない場合は，イラリス 4 mg/kg の 2 回目の追加投与を検討できる。その後，完全寛解が達成された場合は，個々の臨床的判断に応じて維持用量の 8 mg/kg の 8 週ごと投与を検討すること。 4 週未満の投与間隔での投与，あるいは 600 mg 又は 8 mg/kg を超える用量の投与の臨床経験は限定的である。 *4 歳以上、体重 15 kg 以上の成人及び小児* *2 歳以上 4 歳未満の小児、又は* *4 歳以上で体重 7.5 kg 以上 15 kg 未満の小児*

販売名	イラリス 150 mg 凍結乾燥注射剤



スティル病（AOSD 及び SJIA）

体重 7.5 kg 以上のスティル病（AOSD 及び SJIA）患者へのイラリスの推奨用量は 4 mg/kg（最高 300 mg）であり，4 週ごとに皮下投与する。医師は，臨床的改善がみられない患者については，イラリスの投与継続を再検討すること。

痛風性関節炎

適切な尿酸低下薬（ULT）の投与による高尿酸血症の管理を開始するか至適化すること。イラリスは，痛風性関節炎の発作を治療するオン・デマンド療法として投与すること。

成人の痛風性関節炎患者に対するイラリスの推奨用量は 150 mg であり，発作発現時に単回皮下投与する。最大限の効果を得るために，イラリスは痛風性関節炎の発作発現後できる限り速やかに投与すること。

初回投与が無効の患者にはイラリスを再投与しないこと。効果はみられたが再投与が必要な患者には，12 週間以上の間隔を空けた後にイラリスを再投与すること。

特別な患者集団

小児患者集団

CAPS

2 歳未満の CAPS 患者におけるイラリスの安全性及び有効性は確立していない。現在得られているデータは*「望ましくない作用」*，*「薬力学特性」*，*「薬物動態特性」*の項に記載するが，用量として推奨されない。

販売名	イラリス 150 mg 凍結乾燥注射剤
	SJIA 2 歳未満の SJIA 患者におけるイラリスの安全性及び有効性は確立していない。 *通風性関節炎* 小児患者集団には痛風性関節炎を適応症としてイラリスを投与していない。 *高齢者* 用量を調節する必要はない。 *肝機能障害* 肝機能障害を有する患者を対象とした試験は実施していない。 *腎機能障害* 腎機能障害を有する患者において，用量を調節する必要はない。しかし，腎機能障害を有する患者における臨床経験は限られている。 **投与方法** イラリスは皮下投与すること。溶解した溶液の使用及び取扱い上の注意については，*「廃棄及びその他の取扱いに関する特別な注意」の項*を参照のこと。
使用上の注意	**禁忌** 有効成分又は*［「添加物一覧」の項参照］*に記載のいずれかの添加物に対して過敏症のある患者。 重度の活動性感染症のある患者*［「特別な警告及び使用上の注意」の項参照］*。 **特別な警告及び使用上の注意** **感染症** イラリスは重篤な感染症の発現率の増加と関連性がある。したがって，イラリスの投与中及び投与後は，感染症の徴候及び症状を注意深く観察すること。医師は，感染症のある患者，再発性感染症の既往歴のある患者，又は易感染性の状態にある患者にイラリスを投与する場合は十分注意すること。 *CAPS 及びスティル病（AOSD 及びSJIA）の治療* 医療介入の必要な活動性感染症の患者には，イラリスの投与開始又は投与継続をしないこと。 *痛風性関節炎の治療* 活動性感染症の患者にはイラリスを投与しないこと。 重篤な感染症のリスクが増大する恐れがあるため，イラリスと腫瘍壊死因子（TNF）阻害剤は併用しないことが望ましい*［「他剤との相互作用及びその他の相互作用」の項参照］*。 まれなケースとして，イラリスの投与中に異常な感染症又は日和見感染（例：アスペルギルス症，非定型マイコバクテリア感染症，帯状疱疹）の発現が報告されている。イラリスとこれらの事象の因果関係は否定できない。 臨床試験において PPD（精製蛋白誘導物質）皮膚テストを行った CAPS 患者の約 12%はイラリス投与中のフォローアップ検査で陽性反応を示したが，潜在性結核又は活動性結核の臨床所見は認められなかった。

販売名	イラリス 150 mg 凍結乾燥注射剤
	イラリス等のインターロイキン-1（IL-1）阻害剤の投与により，結核の再活性化のリスクが増大するかどうかは不明である。投与開始前に，すべての患者に対し活動性結核及び潜在性結核の評価を行わなければならない。特に成人患者では，詳細な病歴も含めて評価すること。すべての患者に対して，適切なスクリーニングテスト（ツベルクリン検査，インターフェロン-γ 遊離試験又は胸部 X 線検査等）を実施すること（各地域の勧告を適用することもある）。イラリスの投与中及び投与後は，結核の徴候及び症状を注意深く観察しなければならない。すべての患者に対し，イラリスの投与中に結核を示唆する徴候又は症状（持続する咳，体重減少，微熱）があらわれた場合は，医師の診察を受けるように指導すること。PPD テスト結果が陰性から陽性に転じた場合は，特に高リスクの患者は別の方法による結核感染に対するスクリーニング検査を検討すべきある。 **好中球減少症及び白血球減少症** イラリスを含む IL-1 を阻害する医薬品では，好中球減少症（好中球絶対数［ANC］が 1.5×10^9/L 未満）及び白血球減少症の発現が観察されている。好中球減少症又は白血球減少症の患者にはイラリスの投与を開始しないこと。白血球（WBC）数（好中球数を含む）は，投与開始前及び投与開始から 1～2 ヵ月後に評価するのが望ましい。慢性投与又は反復投与についても，本剤投与中は WBC 数を定期的に評価するのが望ましい。患者に好中球減少症又は白血球減少症が発現した場合は，WBC 数を十分に観察するほか，投与中止を検討すること。 **悪性腫瘍** イラリスを投与した患者において，悪性腫瘍の発現が報告されている。抗インターロイキン（IL）-1 療法による悪性腫瘍の発現リスクは不明である。 **過敏症反応** イラリスの投与に対する過敏症反応の発現が報告されている。これらの事象の大半は軽度であった。イラリスの臨床開発では 2,300 例を超える患者が登録されており，アナフィラキシー様症状又はアナフィラキシー反応は報告されていない。しかし，蛋白質の注射剤では重度の過敏症反応が多くみられるため，過敏症反応のリスクは除外できない*［「禁忌」の項参照］*。 **肝機能** 臨床試験では，一過性かつ無症候性の血清トランスアミナーゼ上昇又はビリルビン上昇が報告されている*［「望ましくない作用」の項参照］*。 **ワクチン接種** イラリスを投与中の患者における生（弱毒化）ワクチン接種による二次感染のリスクに関するデータは得られていない。したがって，生ワクチンは，有益性が危険性を明らかに上回ると判断される場合を除き，イラリスと同時に投与すべきではない*［「他剤との相互作用及びその他の相互作用」の項参照］*。 成人及び小児の患者はイラリスの投与開始前に，必要に応じてすべてのワクチン（肺炎球菌ワクチン及びインフルエンザ不活化ワクチンを含む）を接種しておくことが推奨される。 **CAPS 患者における NLRP3 遺伝子変異** NLRP3 遺伝子変異が確認されていない CAPS 患者での臨床経験は限られている。 **スティル病患者におけるマクロファージ活性化症候群** マクロファージ活性化症候群（MAS）は，リウマチ性疾患，特にスティル病患者に発現することのある生命を脅かす障害として知られている。MAS を発症した場合又はその発症が疑われる場合は，できる限り速やかに評価及び治療を開始すること。感染症の症状やスティル病の増悪は MAS を引き起こすことが認められているため，医師はこれらに注意すること。臨床試験の経験では，SJIA 患者にイラリスを投与しても MAS の発現率は増加しないとみられたが，最終的な結論を導き出すことはできない。 **<u>他剤との相互作用及びその他の相互作用</u>** イラリスと他の医薬品の相互作用を検討した，正式な試験は実施されていない。

販売名	イラリス 150 mg 凍結乾燥注射剤
	他の IL-1 阻害薬と TNF 阻害剤の併用投与により，重篤な感染症の発現頻度の増加が認められている。イラリスと TNF 阻害剤の併用でも重篤な感染症発現のリスクが増大する恐れがあるため，併用しないことが望ましい。 肝酵素 CYP450 の発現が，インターロイキン-1β（IL-1β）等の炎症性サイトカインにより抑制されると慢性的な炎症を促す。したがって，カナキヌマブ等の強力なサイトカイン阻害剤の投与により，CYP450 の発現が正常化する可能性がある。治療域が狭く CYP450 の基質が代謝に関連する薬剤において，投与量を個別に調節することは臨床的に意義がある。このような種類の薬剤を投与している患者にカナキヌマブの投与を開始する場合は，効果や有効成分濃度に関するモニタリングを行い，必要に応じて患者ごとに薬剤の投与量を調節する必要がある。 イラリス投与中の患者におけるワクチン接種の影響や生ワクチンによる二次感染に関するデータは得られていない。このため，生ワクチンは，有益性が危険性を明らかに上回ると判断される場合を除いて，イラリスと同時に投与すべきではない。イラリスの投与開始後に生ワクチンの接種が必要となった場合は，イラリスの最終投与日と次回の投与再開日の間隔を 3 ヵ月以上あけることが望ましい *［「特別な警告及び使用上の注意」の項参照］*。 健康成人を対象としたイラリス 300 mg 単回投与試験では，インフルエンザワクチンや糖化蛋白質由来髄膜炎菌ワクチン接種後，抗体反応の誘導や持続性にイラリス投与の影響は見られなかった。 4 歳以下の CAPS 患者を対象とした 56 週オープン投与試験の結果，小児期に接種する標準的な不活化ワクチンを接種した全員が，防御抗体レベルの抗体を発現した。 **<u>受胎能，妊婦及び授乳婦への投与</u>** **妊娠の可能性がある女性／男女の避妊** 女性は，イラリスの投与中及び最終投与後 3 ヵ月間は有効な避妊薬を使用すること。 **妊婦** 妊婦へのカナキヌマブの投与に関するデータ量は限られている。動物実験では，生殖毒性に関する直接的又は間接的な有害な影響は認められていない *［「前臨床安全性データ」の項参照］*。 胎児／母親へのリスクは不明である。したがって，妊婦又は妊娠を希望している女性にイラリスを投与する場合は，綿密なベネフィット・リスク評価を行うこと。 動物試験において，カナキヌマブの胎盤移行及び胎児で検出された。ヒトでのデータはないが，カナキヌマブはイムノグロブリンの G クラス（IgG1）であり，ヒト経胎盤性の移行は予想される。これによる臨床的影響は不明である。しかし，カナキヌマブに *in utero* で曝露された新生児への生ワクチン投与は出産前の母親のイラリス投与から 16 週間は推奨されない。妊娠期間中にイラリスを投与された女性は新生児のワクチン接種について，医師より説明がされる必要がある。 **授乳婦** カナキヌマブがヒトの母乳中に移行するかどうかは不明である。したがって，イラリスの投与は，綿密なベネフィット・リスク評価を行った後にのみ決定すること。 動物実験では，マウス抗マウス IL-1β 抗体はマウス乳児の発育に有害な影響は認められなかったが，乳児に同抗体が移行したとの報告がある *［「前臨床安全性データ」の項参照］*。 **受胎能** ヒトの受胎能に対するイラリスの潜在的影響を検討する正式な試験は実施していない。カナキヌマブは，マーモセット（*C. jacchus*）の雄性受胎能パラメータに影響を及ぼさなかった。マウス抗マウス IL-1β 抗体は，雌雄のマウスの受胎能に望ましくない作用を及ぼさなかった *［「前臨床安全性データ」の項参照］*。 **<u>自動車の運転能及び機械操作能に及ぼす影響</u>**

販売名	イラリス 150 mg 凍結乾燥注射剤

イラリスは，自動車の運転能及び機械操作能にわずかに影響を及ぼす。イラリスの投与により，浮動性めまい／回転性めまい又は無力症があらわれることがある*［「望ましくない作用」の項参照］*。イラリスの投与中にこのような症状が現れた患者は，症状が完全に消失するまで自動車の運転又は機械の操作を行わないこと。

望ましくない作用

安全性プロファイルの概要

CAPS，SJIA，痛風性関節炎又はその他の IL-1β 媒介性疾患の患者，及び健康被験者を対象とした介入試験において，約 380 例の小児（2～17 歳）を含む 2,400 例を超える被験者にイラリスを投与した。重篤な感染症の発現が認められている。最も発現頻度の高かった副作用は，感染症（主に上気道感染）であった。事象の大半は軽度から中等度であった。さらに長期間投与した場合も，副作用の種類又は頻度に対する影響は認められなかった。

イラリスを投与した患者において，過敏症反応の発現が報告されている*［「禁忌」及び「特別な警告及び使用上の注意」の項参照］*。

イラリスを投与した患者において，日和見感染の発現が報告されている*［「特別な警告及び使用上の注意」の項参照］*。

CAPS

臨床試験では，成人及び小児 CAPS 患者（FCAS/FCU，MWS 及び NOMID/CINCA を含む）計 211 例にイラリスを投与した。8 週間の非盲検期（パート I），その後 24 週間の無作為化二重盲検プラセボ対照休薬期（パート II）及び 16 週間の非盲検期（パート III）からなる主要な第 III 相試験において，プラセボとの比較によりイラリスの安全性を検討した。体重 15 kg 以上 40 kg 以下の患者には 2 mg/kg，それ以外の患者にはイラリス 150 mg を皮下投与した。

スティル病

臨床試験において，SJIA 患者（2 歳以上 20 歳未満），2 歳以上 16 歳未満 293 例，16 歳以上 18 歳未満 21 例及び 18 歳以上 20 歳未満 10 例の計 324 例にイラリスを投与した。2 つの主要な第 III 相試験において，プラセボとの比較によりイラリスの安全性を検討した*［「薬力学的特性」の項参照］*。

痛風性関節炎

最長 24 週間の無作為化二重盲検実薬対照試験において，700 例を超える痛風性関節炎患者にイラリス 10 mg～300 mg を投与している。第 II 相及び第 III 相臨床試験において，250 例を超える患者に推奨用量の 150 mg を投与している*［「薬力学的特性」の項参照］*。

副作用の一覧表

副作用は MedDRA の器官別大分類に従って一覧表示している。副作用は，各器官別大分類で分類し，各発現頻度で分類して，最も発現頻度の高かった事象を最初に記載している。発現頻度のカテゴリーは，以下のとおり定義した：極めて高頻度（1/10 以上），高頻度（1/100 以上 1/10 未満），低頻度（1/1,000 以上 1/100 未満），まれ（1/10,000 以上 1/1,000 未満），極めてまれ（1/10,000 未満），不明（入手したデータから推定不可）。副作用は，各発現頻度で分類し，重症度の高いものから順に記載している。

表 1　　CAPS，SJIA 及び痛風性関節炎患者における副作用の一覧表

MedDRA 器官別大分類	CAPS	SJIA	痛風性関節炎
感染症及び寄生虫症			
極めて高頻度	鼻咽頭炎	肺炎，胃腸炎，尿路感染，ウイルス感染，副鼻腔炎，鼻炎，咽頭炎，扁桃炎，鼻咽頭炎，上気道感染	肺炎，気管支炎，胃腸炎，尿路感染，インフルエンザ，蜂巣炎，副鼻腔炎，耳部感染，咽頭炎，鼻咽頭炎，上気道感染

販売名	イラリス 150 mg 凍結乾燥注射剤

高頻度	尿路感染，上気道感染，ウイルス感染		
神経系障害			
高頻度	浮動性めまい／回転性めまい		浮動性めまい／回転性めまい
胃腸障害			
極めて高頻度		腹痛（上腹部）	
低頻度			胃食道逆流性疾患
皮膚及び皮下組織障害			
極めて高頻度	注射部位反応	注射部位反応	
高頻度			注射部位反応
筋骨格系及び結合組織障害			
極めて高頻度		関節痛	
高頻度		筋骨格痛	背部痛
一般・全身障害及び投与部位の状態			
高頻度			疲労／無力症
臨床検査			
極めて高頻度		腎クレアチニン・クリアランス減少 *，蛋白尿 #，白血球減少症	
高頻度		好中球減少症	

*推定クレアチニンクリアランスによると，ほとんどは一過性であった。

大半は試験紙による検査で一過性の尿中蛋白微量～1+陽性であった。

16 歳から 20 歳の若年層の SJIA 患者の部分集団（n=31）において，イラリスの安全性プロファイルは 16 歳未満の SJIA 患者で見られたものと合致していた。AOSD 患者の安全性プロファイルは文献報告より SJIA 患者と類似すると考えられる。

主な副作用の説明

CAPS 患者における長期データ及び臨床検査異常

CAPS 患者を対象としたイラリスの臨床試験では，ヘモグロビンの平均値は増加し，白血球数，好中球数及び血小板数の平均値は減少した。

CAPS 患者では，まれにトランスアミナーゼ上昇が報告されている。

イラリスを投与した CAPS 患者において，トランスアミナーゼ上昇を伴わない，無症候性で軽度の血清ビリルビン上昇が報告されている。

長期非盲検用量漸増試験における感染症（胃腸炎，気道感染，上気道感染），嘔吐及び浮動性めまいの事象の発現頻度は，600 mg 又は 8 mg/kg 投与群の方が他の投与群よりも高いと報告された。

SJIA 患者における臨床検査異常

血液

SJIA のプログラム全体では，33 例の患者（16.5%）において LLN の 0.8 倍以下の一過性の白血球（WBC）数減少が報告された。

SJIA のプログラム全体では，12 例の患者（6.0%）において一過性の好中球絶対数（ANC）減少（1×10^9/L 未満）が報告された。

販売名	イラリス 150 mg 凍結乾燥注射剤
	SJIA のプログラム全体では，19 例の患者（9.5%）において一過性の血小板数減少（LLN 未満）の発現が観察された。 *ALT/AST* SJIA のプログラム全体では，19 例の患者（9.5%）において正常値上限（ULN）の 3 倍を超える ALT 増加及び／又は AST 増加が報告された。 *痛風性関節炎患者における臨床検査異常* *血液* 正常値下限（LLN）の 0.8 倍以下の白血球数（WBC）減少が報告された患者の割合は，イラリス投与患者が 6.7%であったのに対し，トリアムシノロンアセトニド投与患者は 1.4%であった。比較臨床試験では，患者の 2%において 1×10^9/L を下回る好中球絶対数（ANC）減少が報告された。まれなケースとして，0.5×10^9/L を下回る ANC 数も認められた*［「特別な警告及び使用上の注意」の項参照］*。 実薬対照試験の痛風性関節炎患者における軽度（LLN 未満かつ 75×10^9/L を超える）及び一過性の血小板数減少の発現率は，イラリス群（12.7%）の方が比較対照薬群（7.7%）よりも高かった。 *尿酸* 痛風性関節炎の比較臨床試験において，イラリスの投与後に尿酸値上昇（12 週時が 0.7 mg/dL，24 週時が 0.5 mg/dL）が観察された。別の試験では，ULT の服用を開始した患者における尿酸増加は見られなかった。痛風性関節炎以外の患者集団を対象とする臨床試験では，尿酸増加は見られなかった*［「薬力学的特性」の項参照］*。 *ALT/AST* イラリス投与群では，トリアムシノロンアセトニド投与群と比較して，ベースラインから試験終了時までにアラニントランスアミナーゼ（ALT）の平均値及び中央値がそれぞれ 3.0 U/L 及び 2.0 U/L 増加し，アスパラギン酸トランスアミナーゼ（AST）がそれぞれ 2.7 U/L 及び 2.0 U/L 増加した。臨床的に問題となる変化（正常値上限の 3 倍以上）の発現率は，トリアムシノロンアセトニド投与患者（AST 及び ALT とも 2.5%）の方がイラリス投与患者（ALT が 1.6%，AST が 0.8%）よりも高かった。 *トリグリセリド* 痛風性関節炎の実薬対照試験では，イラリス投与患者におけるトリグリセリドの平均増加量は 33.5 mg/dL であったが，トリアムシノロンアセトニ投与患者では-3.1 mg/dL とわずかに減少した。正常値上限（ULN）の 5 倍を超えるトリグリセリド上昇の発現率は，イラリス投与患者が 2.4%，トリアムシノロンアセトニド投与患者が 0.7%であった。本所見の臨床的重要性は不明である。 **小児患者集団** 本試験では，80 例の小児 CAPS 患者（2～17 歳）を組入れた。全体として，イラリスの安全性及び忍容性のプロファイル（感染エピソードの全体的な発現頻度及び重症度を含む）については，小児患者と CAPS 患者集団全体（成人及び小児患者で構成される，211 例）の間に臨床的に有意な差は認められなかった。最も報告の多かった感染症は上気道感染であった。 さらに，2 歳未満の 6 名の小児患者を対象に小規模なオープンラベル臨床試験が実施された。安全性プロファイルは，2 歳以上の患者におけるイラリスの安全性プロファイルと類似していた。 **高齢者集団** 65 歳以上の患者では，安全性プロファイルに有意差は認められていない。 **疑われる副作用の報告** 医薬品承認後に副作用と疑われる事象を報告することは重要である。これにより，医薬品のリスク・ベネフィットバランスを継続的にモニタリングすることができる。医療専門家には，Appendix V に記載の各国の報告システムを通じて，疑われる副作用の報告が求められる。 **過量投与**

販売名	イラリス 150 mg 凍結乾燥注射剤
	過量投与の報告は限られている。初期の臨床試験において，10 mg/kg もの高用量を静脈内投与又は皮下投与した患者及び健康被験者では，急性毒性のエビデンスは認められなかった。 過量投与された場合は，副作用の徴候及び症状について観察し，適切な対症療法を直ちに開始することが望ましい。
改訂年月日	2016 年 8 月 1 日

[redacted]

ILARIS® (canakinumab)

[redacted]

Core Data Sheet (CDS)

[redacted]

[redacted]

[redacted]

[redacted]

2-41頁削除

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ILARIS safely and effectively. See full prescribing information for ILARIS.

ILARIS® (canakinumab) for injection, for subcutaneous use
Initial U.S. Approval: 2009

----------RECENT MAJOR CHANGES----------

Indications and Usage (1.1)	09/2016
Dosage and Administration (2.3, 2.5)	09/2016
Warnings and Precautions, Immunizations (5.4)	07/2016

----------INDICATIONS AND USAGE----------

ILARIS is an interleukin-1β blocker indicated for the treatment of:

Periodic Fever Syndromes:

- **Cryopyrin-Associated Periodic Syndromes (CAPS)**, in adults and children 4 years of age and older including:
  - Familial Cold Autoinflammatory Syndrome (FCAS) (1.1)
  - Muckle-Wells Syndrome (MWS) (1.1)
- **Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS)** in adult and pediatric patients. (1.1)
- **Hyperimmunoglobulin D Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD)** in adult and pediatric patients (1.1)
- **Familial Mediterranean Fever (FMF)** in adult and pediatric patients. (1.1)

Active Systemic Juvenile Idiopathic Arthritis (SJIA) in patients aged 2 years and older (1.2)

----------DOSAGE AND ADMINISTRATION----------

- Administer by subcutaneous injection (2.1)

Cryopyrin-Associated Periodic Syndromes (CAPS)
150 mg for CAPS patients with body weight greater than 40 kg and 2 mg/kg for CAPS patients with body weight greater than or equal to 15 kg and less than or equal to 40 kg. For children 15 to 40 kg with an inadequate response, the dose can be increased to 3 mg/kg. Administer subcutaneously every 8 weeks. (2.2)

Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS), Hyperimmunoglobulin D Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD), and Familial Mediterranean Fever (FMF) (2.3)

- ***Body weight less than or equal to 40 kg***
  - The recommended starting dose is 2 mg/kg every 4 weeks. The dose can be increased to 4 mg/kg every 4 weeks if the clinical response is not adequate.
- ***Body weight greater than 40 kg***
  - The recommended starting dose is 150 mg every 4 weeks. The dose can be increased to 300 mg every 4 weeks if the clinical response is not adequate.

Systemic Juvenile Idiopathic Arthritis (SJIA)
4 mg/kg (with a maximum of 300 mg) for patients with a body weight greater than or equal to 7.5 kg. Administer subcutaneously every 4 weeks. (2.4)

----------DOSAGE FORMS AND STRENGTHS----------

For Injection: 150 mg lyophilized powder in single-dose vials for reconstitution. (3)

----------CONTRAINDICATIONS----------

Confirmed hypersensitivity to the active substance or to any of the excipients. (4)

----------WARNINGS AND PRECAUTIONS----------

- Interleukin-1 blockade may interfere with immune response to infections. Treatment with medications that work through inhibition of IL-1 has been associated with an increased risk of serious infections. ILARIS has been associated with an increased incidence of serious infections. Physicians should exercise caution when administering ILARIS to patients with infections, a history of recurring infections or underlying conditions which may predispose them to infections. Discontinue treatment with ILARIS if a patient develops a serious infection. Do not administer ILARIS to patients during an active infection requiring medical intervention. (5.1)
- Live vaccines should not be given concurrently with ILARIS. Prior to initiation of therapy with ILARIS, patients should receive all recommended vaccinations. (5.4)

----------ADVERSE REACTIONS----------

CAPS: The most common adverse reactions greater than 10% reported by patients treated with ILARIS are nasopharyngitis, diarrhea, influenza, rhinitis, nausea, headache, bronchitis, gastroenteritis, pharyngitis, weight increased, musculoskeletal pain, and vertigo. (6)

TRAPS, HIDS/MKD, and FMF: The most common adverse reactions greater than 10% reported by patients treated with ILARIS are injection site reactions and nasopharyngitis. (6)

SJIA: The most common adverse drug reactions greater than 10% reported by patients treated with ILARIS are infections (nasopharyngitis and upper respiratory tract infections), abdominal pain and injection site reactions. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------DRUG INTERACTIONS----------

No formal drug interaction studies have been conducted with ILARIS. (7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 9/2016

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- 1.2 Systemic Juvenile Idiopathic Arthritis (SJIA)

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Periodic Fever Syndromes

ILARIS (canakinumab) is an interleukin-1β blocker indicated for the treatment of the following autoinflammatory Periodic Fever Syndromes:

Cryopyrin-Associated Periodic Syndromes (CAPS)

ILARIS is indicated for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), in adults and children 4 years of age and older including:

- Familial Cold Autoinflammatory Syndrome (FCAS)
- Muckle-Wells Syndrome (MWS)

Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS)

ILARIS is indicated for the treatment of Tumor Necrosis Factor (TNF) receptor Associated Periodic Syndrome (TRAPS) in adult and pediatric patients.

Hyperimmunoglobulin D Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD)

ILARIS is indicated for the treatment of Hyperimmunoglobulin D (Hyper-IgD) Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD) in adult and pediatric patients.

Familial Mediterranean Fever (FMF)

ILARIS is indicated for the treatment of Familial Mediterranean Fever (FMF) in adult and pediatric patients.

1.2 Systemic Juvenile Idiopathic Arthritis (SJIA)

ILARIS is indicated for the treatment of active Systemic Juvenile Idiopathic Arthritis (SJIA) in patients aged 2 years and older.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

INJECTION FOR SUBCUTANEOUS USE ONLY.

2.2 Cryopyrin-Associated Periodic Syndromes (CAPS)

The recommended dose of ILARIS is 150 mg for CAPS patients with body weight greater than 40 kg. For CAPS patients with body weight greater than or equal to 15 kg and less than or equal to 40 kg, the recommended dose is 2 mg/kg. For children 15 to 40 kg with an inadequate response, the dose can be increased to 3 mg/kg.

ILARIS is administered every eight weeks.

2.3 Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS), Hyperimmunoglobulin D Syndrome/Mevalonate Kinase Deficiency (MKD), and Familial Mediterranean Fever (FMF)

The recommended dose of ILARIS for TRAPS, HIDS/MKD, and FMF patients is based on body weight.

For patients with body weight less than or equal to 40 kg, the recommended dose is 2 mg/kg administered every 4 weeks. The dose can be increased to 4 mg/kg every 4 weeks if the clinical response is not adequate.

For patients with body weight greater than 40 kg, the recommended dose is 150 mg administered every 4 weeks. The dose can be increased to 300 mg every 4 weeks if the clinical response is not adequate.

2.4 Systemic Juvenile Idiopathic Arthritis (SJIA)

The recommended dose of ILARIS for SJIA patients with a body weight greater than or equal to 7.5 kg is 4 mg/kg (with a maximum of 300 mg) administered every 4 weeks.

2.5 Preparation and Administration of ILARIS Lyophilized Powder

STEP 1: Using aseptic technique, reconstitute each vial of ILARIS lyophilized powder by slowly injecting 1 mL of Sterile Water for Injection with a 1-mL syringe and an 18-gauge x 2" needle.

STEP 2: Swirl the vial slowly at an angle of about 45° for approximately 1 minute and allow to stand for 5 minutes. Do not shake. Then gently turn the vial upside down and back again ten times. Avoid touching the rubber stopper with your fingers.

STEP 3: Allow to stand for about 15 minutes at room temperature. The reconstituted solution has a final concentration of 150 mg/mL. Do not shake. Do not use if particulate matter is present in the solution. Tap the side of the vial to remove any residual liquid from the stopper. The reconstituted solution should be clear to opalescent, colorless to a slightly brownish yellow tint, and essentially free from particulates. If the solution has a distinctly brown discoloration, do not use. Slight foaming of the product upon reconstitution is not unusual.

After reconstitution, ILARIS should be kept from light, and can be kept at room temperature if used within 60 minutes of reconstitution. Otherwise, it should be refrigerated at 2°C to 8°C (36°F to 46°F) and used within 4 hours of reconstitution.

STEP 4: Using a sterile 1-mL syringe and needle, carefully withdraw the required volume depending on the dose to be administered and subcutaneously inject using a 27-gauge x 0.5" needle.

Injection into scar tissue should be avoided as this may result in insufficient exposure to ILARIS.

Discard any unused product or waste material in accordance with local requirements.

3 DOSAGE FORMS AND STRENGTHS

For injection: 150 mg lyophilized powder in single-dose vials for reconstitution.

4 CONTRAINDICATIONS

Confirmed hypersensitivity to the active substance or to any of the excipients *[see Warnings and Precautions (5.3) and Adverse Reactions (6.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Serious Infections

ILARIS has been associated with an increased risk of serious infections. Physicians should exercise caution when administering ILARIS to patients with infections, a history of recurring infections or underlying conditions which may predispose them to infections. ILARIS should not be administered to patients during an active infection requiring medical intervention. Administration of ILARIS should be discontinued if a patient develops a serious infection.

Infections, predominantly of the upper respiratory tract, in some instances serious, have been reported with ILARIS. Generally, the observed infections responded to standard therapy. Isolated cases of unusual or opportunistic infections (e.g., aspergillosis, atypical mycobacterial infections, cytomegalovirus, herpes zoster) were reported during ILARIS treatment. A causal relationship of ILARIS to these events cannot be excluded. In clinical trials, ILARIS has not been administered concomitantly with tumor necrosis factor (TNF) inhibitors. An increased incidence of serious infections has been associated with administration of another IL-1 blocker in combination with TNF inhibitors. Coadministration of ILARIS with TNF inhibitors is not recommended because this may increase the risk of serious infections *[see Drug Interactions (7.1)]*.

Drugs that affect the immune system by blocking TNF have been associated with an increased risk of new tuberculosis and reactivation of latent tuberculosis (TB). It is possible that use of IL-1 inhibitors such as ILARIS increases the risk of reactivation of tuberculosis or of opportunistic infections.

Prior to initiating immunomodulatory therapies, including ILARIS, patients should be evaluated for active and latent tuberculosis infection. Appropriate screening tests should be performed in all patients. ILARIS has not been studied in patients with a positive tuberculosis screen, and the safety of ILARIS in individuals with latent tuberculosis infection is unknown. Patients testing positive in tuberculosis screening should be treated according to standard medical practice prior to therapy with ILARIS. All patients should be instructed to seek medical advice if signs, symptoms, or high risk exposure

suggestive of tuberculosis (e.g., persistent cough, weight loss, subfebrile temperature) appear during or after ILARIS therapy.

Healthcare providers should follow current CDC guidelines both to evaluate for and to treat possible latent tuberculosis infections before initiating therapy with ILARIS.

5.2 Immunosuppression

The impact of treatment with anti-interleukin-1 (IL-1) therapy on the development of malignancies is not known. However, treatment with immunosuppressants, including ILARIS, may result in an increase in the risk of malignancies.

5.3 Hypersensitivity

Hypersensitivity reactions have been reported with ILARIS therapy. During clinical trials, no anaphylactic reactions have been reported. It should be recognized that symptoms of the underlying disease being treated may be similar to symptoms of hypersensitivity. ILARIS should not be administered to any patients with known clinical hypersensitivity to ILARIS *[see Contraindications (4) and Adverse Reactions (6.2)]*.

5.4 Immunizations

Live vaccines should not be given concurrently with ILARIS *[see Drug Interactions (7.2)]*. Since no data are available on either the efficacy or on the risks of secondary transmission of infection by live vaccines in patients receiving ILARIS, live vaccines should not be given concurrently with ILARIS. In addition, because ILARIS may interfere with normal immune response to new antigens, vaccinations may not be effective in patients receiving ILARIS. Limited data are available on the response to vaccinations with inactivated (killed) antigens in patients receiving ILARIS *[see Drug Interactions (7.2)]*.

Because IL-1 blockade may interfere with immune response to infections, it is recommended that prior to initiation of therapy with ILARIS, adult and pediatric patients receive all recommended vaccinations, as appropriate and if feasible, including pneumococcal vaccine and inactivated influenza vaccine. (See current recommended immunization schedules at the website of the Centers for Disease Control, http://www.cdc.gov/vaccines/schedules/index.html).

5.5 Macrophage Activation Syndrome

Macrophage activation syndrome (MAS) is a known, life-threatening disorder that may develop in patients with rheumatic conditions, in particular SJIA, and should be aggressively treated. Physicians should be attentive to symptoms of infection or worsening of SJIA, as these are known triggers for MAS. Eleven cases of MAS were observed in 201 SJIA patients treated with canakinumab in clinical trials. Based on the clinical trial experience, ILARIS does not appear to increase the incidence of MAS in SJIA patients, but no definitive conclusion can be made.

6 ADVERSE REACTIONS

Approximately five hundred seventy patients have been treated with ILARIS in interventional trials in CAPS, TRAPS, HIDS/MKD, FMF or SJIA. These clinical trials included approximately 350 children up to 17 years of age. The most frequently reported adverse drug reactions were infections predominantly of the upper respiratory tract. The majority of the events were mild to moderate although serious infections were observed.

Opportunistic infections have also been reported in patients treated with ILARIS *[see Warnings and Precautions (5.1)]*.

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Treatment of Periodic Fever Syndromes: CAPS, TRAPS, HIDS/MKD, and FMF

Treatment of CAPS

The data described herein reflect exposure to ILARIS in 104 adult and pediatric CAPS patients, including 20 FCAS, 72 MWS, 10 MWS/NOMID (Neonatal Onset Multisystem Inflammatory Disorder) overlap, 1 non-FCAS non-MWS, and 1 misdiagnosed in placebo-controlled (35 patients) and uncontrolled trials. Sixty-two patients were exposed to ILARIS for at least 6 months, 56 for at least 1 year, and 4 for at least 3 years. A total of 9 serious adverse reactions were reported for

CAPS patients. Among these were vertigo (2 patients), infections (3 patients), including intra-abdominal abscess following appendectomy (1 patient). The most commonly reported adverse reactions associated with ILARIS treatment in greater than 10% of the CAPS patients were nasopharyngitis, diarrhea, influenza, rhinitis, nausea, headache, bronchitis, gastroenteritis, pharyngitis, weight increased, musculoskeletal pain, and vertigo. One patient discontinued treatment due to potential infection.

CAPS Study 1 investigated the safety of ILARIS in an 8-week, open-label period (Part 1), followed by a 24-week, randomized withdrawal period (Part 2), followed by a 16-week, open-label period (Part 3). All patients were treated with ILARIS 150 mg subcutaneously or 2 mg/kg if body weight was greater than or equal to 15 kg and less than or equal to 40 kg (see Table 1).

Since all CAPS patients received ILARIS in Part 1, there are no controlled data on adverse events (AEs). Data in Table 1 are for all AEs for all CAPS patients receiving canakinumab. In CAPS Study 1, no pattern was observed for any type or frequency of adverse events throughout the three study periods.

Table 1 Number (%) of Patients with AEs by Preferred Terms, in >10% of Patients in Parts 1 to 3 of the Phase 3 Trial for CAPS Patients

Preferred Term	ILARIS N=35 n (%)
n % of Patients with Adverse Events	35 (100)
Nasopharyngitis	12 (34)
Diarrhea	7 (20)
Influenza	6 (17)
Rhinitis	6 (17)
Nausea	5 (14)
Headache	5 (14)
Bronchitis	4 (11)
Gastroenteritis	4 (11)
Pharyngitis	4 (11)
Weight increased	4 (11)
Musculoskeletal pain	4 (11)
Vertigo	4 (11)

Vertigo

Vertigo has been reported in 9% to 14% of patients in CAPS studies, exclusively in MWS patients, and reported as a serious adverse event in two cases. All events resolved with continued treatment with ILARIS.

Injection Site Reactions

In CAPS Study 1, subcutaneous injection site reactions were observed in 9% of patients in Part 1 with mild tolerability reactions; in Part 2, one patient each (7%) had a mild or a moderate tolerability reaction and, in Part 3, one patient had a mild local tolerability reaction. No severe injection-site reactions were reported and none led to discontinuation of treatment.

Treatment of TRAPS, HIDS/MKD, and FMF

A Phase III trial (TRAPS, HIDS/MKD, and FMF Study 1) investigated the safety of ILARIS in 3 cohorts (TRAPS, HIDS/MKD, and FMF) as follows: a 12-week screening period (Part 1), followed by a 16-week, randomized, double-blind, placebo-controlled parallel-arm treatment period (Part 2), followed by a 24-week randomized withdrawal period (Part 3), followed by a 72-week, open-label treatment period (Part 4). All patients randomized to treatment with ILARIS in Part 2 received 150 mg subcutaneously every 4 weeks if body weight was greater than 40 kg (or 2 mg/kg every 4 weeks if body weight was less than or equal to 40 kg).

In Part 2 of the TRAPS, HIDS/MKD, and FMF Study 1, initially 90 patients were randomized to ILARIS treatment and 91 patients were randomized to placebo. Of patients randomized to ILARIS, 55.6% remained on the initial dose through week 16 with 6.7% receiving an additional ILARIS dose between Day 7 and Day 15. Of the patients randomized to placebo, 9.9% remained on placebo through Week 16 with 28.6% switching to active treatment with ILARIS by Day 15.

Overall, there were 43 TRAPS, 68 HIDS/MKD, and 58 FMF patients in the Safety set with a cumulative canakinumab exposure of 47.61 patient-years. The cumulative exposure in the placebo group was 8.03 patient-years.

In Part 2 of the TRAPS, HIDS/MKD, and FMF Study 1, a total of 22 TRAPS patients aged 3 to 76 years of age, 37 HIDS/MKD patients aged 2 to 43 years of age, and 31 FMF patients aged 2 to 60 years of age were initially randomized to treatment with ILARIS 150 mg every four weeks in the placebo-controlled period of the clinical trial. In addition, 4 non-randomized patients (2 FMF patients of age 20 and 29 years with non-exon 10 mutations and 2 HIDS/MKD patients both of 1 year of age) received open-label treatment in Part 2.

The most commonly reported adverse reactions (greater than or equal to 10%) associated with ILARIS treatment in TRAPS, HIDS/MKD, and FMF patients were injection site reactions and nasopharyngitis. The reported adverse reactions (greater than or equal to 3%) associated with ILARIS treatment in TRAPS, HIDS/MKD, and FMF patients were injection site reactions (10.1%), and infections including nasopharyngitis (10.7%), upper respiratory tract infection (7.1%), rhinitis (5.3%), gastroenteritis (3.0%), and pharyngitis (3.0%). Serious infections (e.g., conjunctivitis, pneumonia, pharyngitis, pharyngotonsillitis) were observed in approximately 2.4% (0.03 per 100 patient-days) of patients receiving ILARIS in part 2 of the TRAPS, HIDS/MKD, and FMF Study 1.

In the ILARIS treatment group, 1 TRAPS patient discontinued treatment due to adverse events, 2 HIDS/MKD patients discontinued treatment due to adverse events, and no FMF patients discontinued treatment due to an adverse event.

Injection Site Reactions

In the TRAPS, HIDS/MKD, and FMF Study 1, subcutaneous injection site reactions were observed in 10.1% of patients in Part 2 who had a mild or a moderate tolerability reaction. No severe injection-site reactions were reported and none led to discontinuation of treatment.

Treatment of SJIA

A total of 201 SJIA patients aged 2 to less than 20 years have received ILARIS in clinical trials. The safety of ILARIS compared to placebo was investigated in two phase 3 studies *[see Clinical Studies (14.2)]*. Patients in SJIA Study 1 received a single dose of ILARIS 4 mg/kg (n=43) or placebo (n=41) via subcutaneous injection and were assessed at Day 15 for the efficacy endpoints and had a safety analysis up to Day 29. SJIA Study 2 was a two-part study with an open-label, single-arm active treatment period (Part I) followed by a randomized, double-blind, placebo-controlled, event-driven withdrawal design (Part II). Overall, 177 patients were enrolled into the study and received ILARIS 4 mg/kg (up to 300 mg maximum) in Part I, and 100 patients received ILARIS 4 mg/kg (up to 300 mg maximum) every 4 weeks or placebo in Part II. Adverse drug reactions listed in Table 2 showed higher rates than placebo from both trials. The adverse drug reactions associated with ILARIS treatment in greater than 10% of SJIA patients were infections, abdominal pain, and injection site reactions. Serious infections (e.g., pneumonia, varicella, gastroenteritis, measles, sepsis, otitis media, sinusitis, adenovirus, lymph node abscess, pharyngitis) were observed in approximately 4% to 5% (0.02 to 0.17 per 100 patient-days) of patients receiving ILARIS in both studies.

Adverse reactions are listed according to MedDRA version 15.0 system organ class.

Table 2 Tabulated Summary of Adverse Drug Reactions from Pivotal SJIA Clinical Trials

	SJIA Study 2			SJIA Study 1	
	Part I	**Part II**			
	ILARIS N=177 n (%) (IR)^	ILARIS N=50 n (%) (IR)	Placebo N=50 n (%) (IR)	ILARIS N=43 n (%) (IR)	Placebo N=41 n (%) (IR)
Infections and infestations					
All Infections (e.g., nasopharyngitis, (viral) upper respiratory tract infection, pneumonia, rhinitis, pharyngitis, tonsillitis, sinusitis, urinary tract infection, gastroenteritis, viral infection)	97 (54.8%) (0.91)	27 (54%) (0.59)	19 (38%) (0.63)	13 (30.2%) (1.26)	5 (12.2%) (1.37)
Gastrointestinal disorders					
Abdominal pain (upper)	25 (14.1%) (0.16)	8 (16%) (0.15)	6 (12%) (0.08)	3 (7%) (0.25)	1 (2.4%) (0.23)
Skin and subcutaneous tissue disorders					
Injection site reaction*					
mild	19 (10.7%)	6 (12.0%)	2 (4.0%)	0	3 (7.3%)
moderate	2 (1.1%)	1 (2.0%)	0	0	0

n= number of patients

^ IR=Exposure adjusted incidence rate per 100 patient-days

* No injection site reaction led to study discontinuation

6.2 Hypersensitivity

During clinical trials, no anaphylactic reactions have been reported. In CAPS trials one patient discontinued and in TRAPS, HIDS/MKD, FMF, and SJIA trials no patients discontinued due to hypersensitivity reactions. ILARIS should not be administered to any patients with known clinical hypersensitivity to ILARIS *[see Contraindications (4) and Warnings and Precautions (5.3)]*.

6.3 Immunogenicity

A biosensor binding assay or a bridging immunoassay was used to detect antibodies directed against canakinumab in patients who received ILARIS. Antibodies against ILARIS were observed in approximately 1.5% and 3.1% of the patients treated with ILARIS for CAPS and SJIA, respectively. No neutralizing antibodies were detected. No apparent correlation of antibody development to clinical response or adverse events was observed. The CAPS clinical studies employed the biosensor binding assay, and most of the SJIA clinical studies employed the bridging assay. The data obtained in an assay are highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, underlying disease, and the number of patients tested. For these reasons, comparison of the incidence of antibodies to canakinumab between the CAPS and SJIA clinical studies or with the incidence of antibodies to other products may be misleading.

No TRAPS, HIDS/MKD and FMF patients treated with ILARIS doses of 150 mg and 300 mg over 16 weeks of treatment tested positive for anti-canakinumab antibodies.

6.4 Laboratory Findings

Hematology

TRAPS, HIDS/MKD, and FMF

Overall, in the TRAPS, HIDS/MKD, and FMF Study 1, neutrophil count decreased (≥Grade 2) was reported in 6.5% of patients and platelet count decreased (≥Grade 2) was reported in 0.6% of patients.

SJIA

During clinical trials with ILARIS, mean values decreased for white blood cells, neutrophils and platelets.

In the randomized, placebo-controlled portion of SJIA Study 2 decreased white blood cell counts (WBC) less than or equal to 0.8 times lower limit of normal (LLN) were reported in 5 patients (10.4%) in the ILARIS group compared to 2 (4.0%) in the placebo group. Transient decreases in absolute neutrophil count (ANC) to less than $1x10^9$/L were reported in 3 patients (6.0%) in the ILARIS group compared to 1 patient (2.0%) in the placebo group. One case of ANC less than $0.5x10^9$/L was observed in the ILARIS group and none in the placebo group.

Mild (less than LLN and greater than $75x10^9$/L) and transient decreases in platelet counts were observed in 3 (6.3%) ILARIS-treated patients versus 1 (2.0%) placebo-treated patient.

Hepatic Transaminases

Elevations of transaminases have been observed in patients treated with ILARIS.

In the randomized, placebo-controlled portion of SJIA Study 2, high ALT and/or AST greater than or equal to 3 times upper limit of normal (ULN) were reported in 2 (4.1%) ILARIS-treated patients and 1 (2.0%) placebo patient. All patients had normal values at the next visit.

Bilirubin

Asymptomatic and mild elevations of serum bilirubin have been observed in patients treated with ILARIS without concomitant elevations of transaminases.

7 DRUG INTERACTIONS

Interactions between ILARIS and other medicinal products have not been investigated in formal studies.

7.1 TNF-Blocker and IL-1 Blocking Agent

An increased incidence of serious infections and an increased risk of neutropenia have been associated with administration of another IL-1 blocker in combination with TNF inhibitors in another patient population. Use of ILARIS with TNF inhibitors may also result in similar toxicities and is not recommended because this may increase the risk of serious infections *[see Warnings and Precautions (5.1)]*.

The concomitant administration of ILARIS with other drugs that block IL-1 has not been studied. Based upon the potential for pharmacological interactions between ILARIS and a recombinant IL-1ra, concomitant administration of ILARIS and other agents that block IL-1 or its receptors is not recommended.

7.2 Immunization

No data are available on either the effects of live vaccination or the secondary transmission of infection by live vaccines in patients receiving ILARIS. Therefore, live vaccines should not be given concurrently with ILARIS. It is recommended that, if possible, pediatric and adult patients should complete all immunizations in accordance with current immunization guidelines prior to initiating ILARIS therapy *[see Warnings and Precautions (5.4)]*.

7.3 Cytochrome P450 Substrates

The formation of CYP450 enzymes is suppressed by increased levels of cytokines (e.g., IL-1) during chronic inflammation. Thus it is expected that for a molecule that binds to IL-1, such as canakinumab, the formation of CYP450 enzymes could be normalized. This is clinically relevant for CYP450 substrates with a narrow therapeutic index, where the dose is individually adjusted (e.g., warfarin). Upon initiation of canakinumab, in patients being treated with these types of medicinal products, therapeutic monitoring of the effect or drug concentration should be performed and the individual dose of the medicinal product may need to be adjusted as needed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The limited human data from postmarketing reports on use of ILARIS in pregnant women are not sufficient to inform a drug associated risk. Monoclonal antibodies, such as canakinumab, are transported across the placenta in a linear fashion as pregnancy progresses; therefore, potential fetal exposure is likely to be greater during the second and third trimesters of pregnancy. In animal embryo-fetal development studies with marmoset monkeys, there was no evidence of embryotoxicity or fetal malformations with subcutaneous administration of canakinumab during the period of organogenesis and later in gestation at doses that produced exposures approximately 11 times the exposure at the maximum recommended human dose (MRHD) and greater. Delays in fetal skeletal development were observed in marmoset monkeys following prenatal exposure to ILARIS at concentrations approximately 11 times the MRHD and greater. Similar delays in fetal skeletal development were observed in mice administered a murine analog of ILARIS during the period of organogenesis. Delays in skeletal ossification are changes from the expected ossification state in an otherwise normal structure/bone: these findings are generally reversible or transitory and not detrimental to postnatal survival *[see Animal Data]*.

The estimated background risk of major birth defects and miscarriage for the indicated population(s) are unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

In embryo-fetal development studies, pregnant marmoset monkeys received canakinumab from gestation days 25 to 140 at doses that produced exposures approximately 11 times that achieved with MRHD and greater (on a plasma AUC basis with maternal subcutaneous doses of 15, 50, or 150 mg/kg twice weekly). ILARIS did not elicit any evidence of embryotoxicity or fetal malformations. There were increases in the incidence of incomplete ossification of the terminal caudal vertebra and misaligned and/or bipartite vertebra in fetuses at all dose levels when compared to concurrent controls suggestive of delay in skeletal development in the marmoset. Since ILARIS does not cross-react with mouse or rat IL-1β, pregnant mice were subcutaneously administered a murine analog of ILARIS at doses of 15, 50, or 150 mg/kg during the period of organogenesis on gestation days 6, 11, and 17. The incidence of incomplete ossification of the parietal and frontal skull bones of fetuses was increased in a dose-dependent manner at all dose levels tested.

8.2 Lactation

Risk Summary

There is no information regarding the presence of canakinumab in human milk, the effects on the breastfed infant, or the effects on milk production. Human IgG is known to be present in human milk. The effects of canakinumab in breast milk and possible systemic exposure in the breastfed infant are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ILARIS and any potential adverse effects on the breastfed infant from canakinumab or from the underlying maternal condition.

8.4 Pediatric Use

The CAPS trials with ILARIS included a total of 23 pediatric patients with an age range from 4 years to 17 years (11 adolescents were treated subcutaneously with 150 mg, and 12 children were treated with 2 mg/kg based on body weight greater than or equal to 15 kg and less than or equal to 40 kg). The majority of patients achieved improvement in clinical symptoms and objective markers of inflammation (e.g., Serum Amyloid A and C-Reactive Protein). Overall, the efficacy and safety of ILARIS in pediatric and adult patients were comparable. Infections of the upper respiratory tract were the most frequently reported infection. The safety and effectiveness of ILARIS in CAPS patients under 4 years of age has not been established *[see Pharmacokinetics (12.3)]*.

The safety and efficacy of ILARIS in SJIA patients under 2 years of age have not been established *[see Pharmacokinetics (12.3)]*.

The TRAPS, HIDS/MKD, and FMF trial included a total of 102 pediatric patients (TRAPS, HIDS/MKD and FMF patients) with an age range from 2 to 17 years who received ILARIS. Overall, there were no clinically meaningful differences in the efficacy, safety and tolerability profile of ILARIS in pediatric patients compared to the overall TRAPS, HIDS/MKD, and FMF populations (comprised of adult and pediatric patients, N=169). The majority of pediatric patients achieved improvement in clinical symptoms and objective markers of inflammation.

8.5 Geriatric Use

Clinical studies of ILARIS did not include sufficient numbers of subjects aged 65 years and older to determine whether they respond differently from younger subjects.

8.6 Patients with Renal Impairment

No formal studies have been conducted to examine the pharmacokinetics of ILARIS administered subcutaneously in patients with renal impairment.

8.7 Patients with Hepatic Impairment

No formal studies have been conducted to examine the pharmacokinetics of ILARIS administered subcutaneously in patients with hepatic impairment.

10 OVERDOSAGE

No confirmed case of overdose has been reported. In the case of overdose, it is recommended that the subject be monitored for any signs and symptoms of adverse reactions or effects, and appropriate symptomatic treatment be instituted immediately.

11 DESCRIPTION

Canakinumab is a recombinant, human anti-human-IL-1β monoclonal antibody that belongs to the IgG1/κ isotype subclass. It is expressed in a murine Sp2/0-Ag14 cell line and comprised of two 447- (or 448-) residue heavy chains and two 214-residue light chains, with a molecular mass of 145157 Daltons when deglycosylated. Both heavy chains of canakinumab contain oligosaccharide chains linked to the protein backbone at asparagine 298 (Asn 298).

The biological activity of canakinumab is measured by comparing its inhibition of IL-1β-dependent expression of the reporter gene luciferase to that of a canakinumab internal reference standard, using a stably transfected cell line.

ILARIS (canakinumab) for Injection is supplied as a white, preservative-free, lyophilized powder in a sterile, single-dose, colorless, glass vial with coated stopper and aluminum flip-off cap. Reconstitution with 1 mL of Sterile Water for Injection is required prior to subcutaneous administration of the drug. The reconstituted canakinumab is a 150 mg/mL solution essentially free of particulates, clear to opalescent, and is colorless or may have a slightly brownish-yellow tint. A volume of up to 1 mL can be withdrawn for delivery of 150 mg canakinumab, L-histidine (2.8 mg), L-histidine HCl monohydrate (1.7 mg), polysorbate 80 (0.6 mg), sucrose (92.4 mg), and Sterile Water for Injection.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Canakinumab is a human monoclonal anti-human IL-1β antibody of the IgG1/κ isotype. Canakinumab binds to human IL-1β and neutralizes its activity by blocking its interaction with IL-1 receptors, but it does not bind IL-1α or IL-1 receptor antagonist (IL-1ra).

CAPS refer to rare genetic syndromes generally caused by mutations in the NLRP-3 [nucleotide-binding domain, leucine rich family (NLR), pyrin domain containing 3] gene (also known as Cold-Induced Auto-inflammatory Syndrome-1 [CIAS1]). CAPS disorders are inherited in an autosomal dominant pattern with male and female offspring equally affected. Features common to all disorders include fever, urticaria-like rash, arthralgia, myalgia, fatigue, and conjunctivitis.

The NLRP-3 gene encodes the protein cryopyrin, an important component of the inflammasome. Cryopyrin regulates the protease caspase-1 and controls the activation of interleukin-1 beta (IL-1β). Mutations in NLRP-3 result in an overactive inflammasome resulting in excessive release of activated IL-1β that drives inflammation. Systemic juvenile idiopathic

arthritis (SJIA) is a severe autoinflammatory disease, driven by innate immunity by means of pro-inflammatory cytokines such as interleukin 1β (IL-1β).

12.2 Pharmacodynamics

C-reactive protein and Serum Amyloid A (SAA) are indicators of inflammatory disease activity that are elevated in patients with CAPS. Elevated SAA has been associated with the development of systemic amyloidosis in patients with CAPS. Following ILARIS treatment, CRP and SAA levels normalize within 8 days. In SJIA the median percent reduction in CRP from baseline to Day 15 was 91%. Improvement in pharmacodynamic markers may not be representative of clinical response.

12.3 Pharmacokinetics

Absorption

The peak serum canakinumab concentration (C_{max}) of 16 ± 3.5 mcg/mL occurred approximately 7 days after subcutaneous administration of a single, 150 mg dose subcutaneously to adult CAPS patients. The mean terminal half-life was 26 days. The absolute bioavailability of subcutaneous canakinumab was estimated to be 66%. Exposure parameters (such as AUC and C_{max}) increased in proportion to dose over the dose range of 0.30 to 10 mg/kg given as intravenous infusion or from 150 to 300 mg as subcutaneous injection.

Distribution

Canakinumab binds to serum IL-1β. Canakinumab volume of distribution (Vss) varied according to body weight and was estimated to be 6.01 liters in a typical CAPS patient weighing 70 kg, 3.2 liters in a SJIA patient weighing 33 kg, and 6.34 liters for a Periodic Fever Syndrome (TRAPS, HIDS/MKD, FMF) patient weighing 70 kg. The expected accumulation ratio was 1.3-fold for CAPS patients and 1.6-fold for SJIA patients following 6 months of subcutaneous dosing of 150 mg ILARIS every 8 weeks and 4 mg/kg every 4 weeks, respectively.

Elimination

Clearance (CL) of canakinumab varied according to body weight and was estimated to be 0.174 L/day in a typical CAPS patient weighing 70 kg, 0.11 L/day in a SJIA patient weighing 33 kg, and 0.17 L/day in a Periodic Fever Syndrome (TRAPS, HIDS/MKD, FMF) patient weighing 70 kg. There was no indication of accelerated clearance or time-dependent change in the pharmacokinetic properties of canakinumab following repeated administration. No gender- or age-related pharmacokinetic differences were observed after correction for body weight.

Pediatrics

Pharmacokinetic properties are similar in Periodic Fever Syndromes (CAPS, TRAPS, HIDS/MKD, FMF) and SJIA pediatric populations. In patients less than 2 years of age (n=7), the exposure of canakinumab were comparable to older age groups with the same weight based dose.

In CAPS patients, peak concentrations of canakinumab occurred between 2 to 7 days following single subcutaneous administration of ILARIS 150 mg or 2 mg/kg in pediatric patients. The terminal half-life ranged from 22.9 to 25.7 days, similar to the pharmacokinetic properties observed in adults.

In SJIA, exposure parameters (such as AUC and C_{max}) were comparable across age groups from 2 years of age and above following subcutaneous administration of canakinumab 4 mg/kg every 4 weeks.

In TRAPS, HIDS/MKD, and FMF exposure parameter trough concentrations were comparable across age groups from 2 to less than 20 years following subcutaneous administration of canakinumab 2 mg/kg every 4 weeks.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential of canakinumab.

As canakinumab does not cross-react with rodent IL-1β, male and female fertility was evaluated in a mouse model using a murine analog of canakinumab. Male mice were treated weekly beginning 4 weeks prior to mating and continuing through 3 weeks after mating. Female mice were treated weekly for 2 weeks prior to mating through gestation day 3 or 4. The

murine analog of canakinumab did not alter either male or female fertility parameters at subcutaneous doses up to 150 mg/kg.

14 CLINICAL STUDIES

14.1 Treatment of CAPS

The efficacy and safety of ILARIS for the treatment of CAPS was demonstrated in CAPS Study 1, a 3-part trial in patients 9 to 74 years of age with the MWS phenotype of CAPS. Throughout the trial, patients weighing more than 40 kg received ILARIS 150 mg and patients weighing 15 to 40 kg received 2 mg/kg. Part 1 was an 8-week open-label, single-dose period where all patients received ILARIS. Patients who achieved a complete clinical response and did not relapse by Week 8 were randomized into Part 2, a 24-week randomized, double-blind, placebo-controlled withdrawal period. Patients who completed Part 2 or experienced a disease flare entered Part 3, a 16-week open-label active treatment phase. A complete response was defined as ratings of minimal or better for physician's assessment of disease activity (PHY) and assessment of skin disease (SKD) and had serum levels of C-Reactive Protein (CRP) and Serum Amyloid A (SAA) less than 10 mg/L. A disease flare was defined as a CRP and/or SAA values greater than 30 mg/L and either a score of mild or worse for PHY or a score of minimal or worse for PHY and SKD.

In Part 1, a complete clinical response was observed in 71% of patients one week following initiation of treatment and in 97% of patients by Week 8 (see Table 3 and Figure 1). In the randomized withdrawal period, a total of 81% of the patients randomized to placebo flared as compared to none (0%) of the patients randomized to ILARIS. The 95% confidence interval for treatment difference in the proportion of flares was 53% to 96%. At the end of Part 2, all 15 patients treated with ILARIS had absent or minimal disease activity and skin disease (see Table 3).

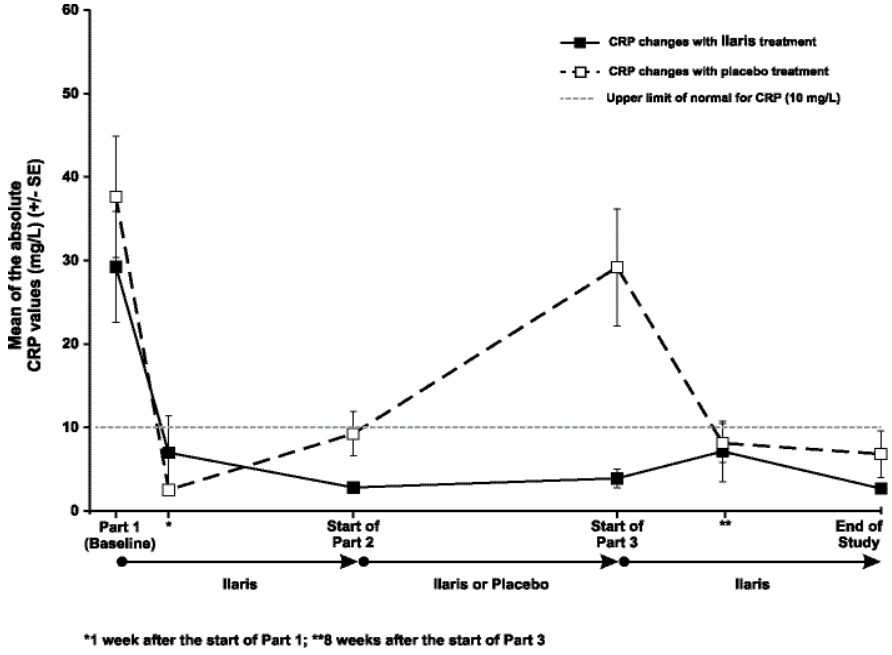
In a second trial, patients 4 to 74 years of age with both MWS and FCAS phenotypes of CAPS were treated in an open-label manner. Treatment with ILARIS resulted in clinically significant improvement of signs and symptoms and in normalization of high CRP and SAA in a majority of patients within 1 week.

Table 3 Physician's Global Assessment of Auto-Inflammatory Disease Activity and Assessment of Skin Disease: Frequency Table and Treatment Comparison in Part 2 (Using LOCF, ITT Population)

		ILARIS N=15		Placebo N=16	
	Baseline	**Start of Part 2 (Week 8)**	**End of Part 2**	**Start of Part 2 (Week 8)**	**End of Part 2**
Physician's Global Assessment of Auto-Inflammatory Disease Activity – n (%)					
Absent	0/31 (0)	9/15 (60)	8/15 (53)	8/16 (50)	0/16 (0)
Minimal	1/31 (3)	4/15 (27)	7/15 (47)	8/16 (50)	4/16 (25)
Mild	7/31 (23)	2/15 (13)	0/15 (0)	0/16 (0)	8/16 (50)
Moderate	19/31 (61)	0/15 (0)	0/15 (0)	0/16 (0)	4/16 (25)
Severe	4/31 (13)	0/15 (0)	0/15 (0)	0/16 (0)	0/16 (0)
Assessment of Skin Disease – n (%)					
Absent	3/31 (10)	13/15 (87)	14/15 (93)	13/16 (81)	5/16 (31)
Minimal	6/31 (19)	2/15 (13)	1/15 (7)	3/16 (19)	3/16 (19)
Mild	9/31 (29)	0/15 (0)	0/15 (0)	0/16 (0)	5/16 (31)
Moderate	12/31 (39)	0/15 (0)	0/15 (0)	0/16 (0)	3/16 (19)
Severe	1/32 (3)	0/15 (0)	0/15 (0)	0/16 (0)	0/16 (0)

Markers of inflammation CRP and SAA normalized within 8 days of treatment in the majority of patients. Normal mean CRP (Figure 1) and SAA values were sustained throughout CAPS Study 1 in patients continuously treated with canakinumab. After withdrawal of canakinumab in Part 2 CRP (Figure 1) and SAA values again returned to abnormal values and subsequently normalized after reintroduction of canakinumab in Part 3. The pattern of normalization of CRP and SAA was similar.

Figure 1. Mean C-Reactive Protein Levels at the End of Parts 1, 2 and 3 of CAPS Study 1



*1 week after the start of Part 1; **8 weeks after the start of Part 3

14.2 Treatment of Periodic Fever Syndromes: TRAPS, HIDS/MKD, and FMF

The efficacy and safety of ILARIS for the treatment of TRAPS, HIDS/MKD, and FMF was demonstrated in a 4-Part study (TRAPS, HIDS/MKD, and FMF Study 1) consisting of three separate, disease cohorts (TRAPS, HIDS/MKD and FMF) which enrolled 185 patients aged greater than 28 days. Patients in each cohort entered a 12-week screening period

(Part 1) during which they were evaluated for the onset of disease flare. Patients aged 2 to 76 years were then randomized at flare onset into a 16-week double-blind, placebo-controlled treatment period (Part 2) where they received either 150 mg ILARIS (2 mg/kg for patients weighing less than or equal to 40 kg) subcutaneously or placebo every 4 weeks. Part 3 and Part 4 of this study are ongoing.

Randomized patients in Part 2 treated with ILARIS whose disease flare did not resolve, or who had persistent disease activity from Day 8 up to Day 14 (Physician's Global Assessment (PGA) greater than or equal to 2 or C-reactive Protein (CRP) greater than 10 mg/L and no reduction by at least 40% from baseline) received an additional dose of 150 mg (or 2 mg/kg for patients weighing less than or equal to 40 kg). Patients treated with ILARIS whose disease flare did not resolve, or who had persistent disease activity from Day 15 up to Day 28 (PGA greater than or equal to 2 or CRP greater than 10 mg/L and no reduction by at least 70% from baseline), also received an additional dose of 150 mg (or 2 mg/kg for patients weighing less than or equal to 40 kg). On or after Day 29, patients treated with ILARIS in Part 2 with PGA greater than or equal to 2 and CRP greater than or equal to 30 mg/L were also up-titrated. All up-titrated patients remained at the increased dose of 300 mg (or 4 mg/kg for patients weighing less than or equal to 40 kg) every 4 weeks.

The primary efficacy endpoint of the randomized, 16-week treatment period (Part 2) was the proportion of complete responders within each cohort as defined by patients who had resolution of their index disease flare at Day 15 and did not experience a new disease flare during the remainder of the 16-week treatment period. Resolution of the index disease flare (initial flare at the time of the randomization) was defined at the Day 15 visit as a Physician's Global Assessment (PGA) Disease Activity score less than 2 ("minimal or no disease") and C-reactive Protein (CRP) within normal range (less than or equal to 10 mg/L) or reduction greater than or equal to 70% from baseline. The key signs and symptoms assessed in the PGA for each condition were the following: TRAPS: abdominal pain, skin rash, musculoskeletal pain, eye manifestations; HIDS/MKD: abdominal pain; lymphadenopathy, aphthous ulcers; FMF: abdominal pain, skin rash, chest pain, arthralgia/arthritis. A new flare was defined as a PGA score greater than or equal to 2 ("mild, moderate, or severe disease") and CRP greater to or equal than 30 mg/L. In the 16-week treatment period (Part 2), patients who needed dose escalation, who crossed over from placebo to ILARIS, or who discontinued from the study due to any reason prior to Week 16 were considered as non-responders.

Patients randomized in the TRAPS cohort (N=46) were aged 2 to 76 years (median age at baseline: 15.5 years) and of this population, 57.8% did not have fever at baseline. Randomized TRAPS patients were those with chronic or recurrent disease activity defined as 6 flares per year (median number of flares per year: 9.0) with PGA greater than or equal to 2 and CRP greater than 10 mg/L (median CRP at baseline: 112.5 mg/L). In the TRAPS cohort, 11/22 (50.0%) patients randomized to ILARIS 150 mg q4w received up-titration to 300 mg q4w during the 16-week treatment period, while 21/24 (87.5%) patients randomized to placebo crossed over to ILARIS.

Patients randomized in the HIDS/MKD cohort (N=72) were aged 2 to 47 years (median age at baseline: 11.0 years) and of this population, 41.7% did not have fever at baseline. Randomized HIDS/MKD patients were those with a confirmed diagnosis of HIDS according to known genetic MVK/enzymatic (MKD) findings, and documented prior history of greater than or equal to 3 febrile acute flares within a 6 month period (median number of flares per year: 12.0) when not receiving prophylactic treatment and during the study, had active HIDS flares defined as PGA greater than or equal to 2 and CRP greater than 10 mg/L (median CRP at baseline: 113.5 mg/L). In the HIDS/MKD cohort, 19/37 (51.4%) patients randomized to ILARIS 150 mg q4w received up-titration to 300 mg q4w during the 16-week treatment period, while 31/35 (88.6%) patients randomized to placebo crossed over to ILARIS.

Patients randomized in the FMF cohort (N=63) were aged 2 to 69 years (median age at baseline: 18.0 years) and of this population, 76.2% did not have fever at baseline. Randomized FMF patients were those with documented active disease despite colchicine therapy or documented intolerance to effective doses of colchicine. Patients had active disease defined as at least one flare per month (median number of flares per year: 18.0) and CRP greater than 10 mg/L (median CRP at baseline: 94.0 mg/L). Patients were allowed to continue their stable dose of colchicine without change. Of the 63 randomized patients, 55 (87.3%) were taking concomitant colchicine therapy on or after randomization. In the FMF cohort, 10/31 (32.3%) patients randomized to ILARIS 150 mg q4w received up-titration to 300 mg q4w during the 16-week treatment period, while 27/32 (84.4%) patients randomized to placebo crossed over to ILARIS.

For the primary efficacy endpoint, ILARIS was superior to placebo in the proportion of TRAPS, HIDS/MKD, and FMF patients who resolved their index disease flare at Day 15 and had no new flare over the 16 weeks of treatment from the time of the resolution of the index flare (see Table 4).

Table 4 Proportion of TRAPS, HIDS/MKD, and FMF Patients Who Achieved a Complete Response (Resolution of Index Flare by Day 15 and Maintained Through Week 16)

	ILARIS 150 mg	Placebo	Treatment comparison	
Cohort	**n/N (%)**	**n/N (%)**	**Odds Ratio 95% CI**	**p-value**
TRAPS	10/22 (45.5%)	2/24 (8.3%)	9.17 (1.51, 94.61)	0.005
HIDS/MKD	13/37 (35.1%)	2/35 (5.7%)	8.94 (1.72, 86.41)	0.002
FMF	19/31 (61.3%)	2/32 (6.3%)	23.75 (4.38, 227.53)	<0.0001

n=number of patients with the response; N=number of patients evaluated for that response in each cohort; CI: Confidence Interval.

At Day 15, a higher proportion of ILARIS-treated patients compared to placebo-treated patients experienced resolution of their index flare in all disease cohorts (see Table 5).

Table 5 Resolution of Index Flare (Full Analysis Set)

	Resolution at Day 15*	
	ILARIS 150 mg Q4W	**Placebo**
Variable	**n/N (%)**	**n/N (%)**
TRAPS	14/22 (63.6%)	5/24 (20.8%)
HIDS/MKD	24/37 (64.9%)	13/35 (37.1%)
FMF	25/31 (80.7%)	10/32 (31.3%)

n=number of patients with the response; N=number of patients evaluated for that response in each cohort
*Resolution of index disease flare (PGA less than 2 and CRP less than or equal to 10 mg/L or reduction greater than or equal to 70% from baseline)

There was supportive evidence of efficacy for ILARIS at Day 15, as compared to placebo, for the components of the primary endpoint, CRP and PGA Disease Activity score, as well as for the secondary endpoint Serum Amyloid A (SAA) level (see Table 6).

Table 6 Proportion of TRAPS, HIDS/MKD, and FMF Patients Achieving PGA<2, CRP ≤10 mg/L and SAA ≤10 mg/L at Day 15*

	TRAPS			HIDS/MKD			FMF		
Variable	**ILARIS 150 mg**	**Placebo**	**Treatment comparison**	**ILARIS 150 mg**	**Placebo**	**Treatment comparison**	**ILARIS 150 mg**	**Placebo**	**Treatment comparison**
	n/N (%)	**n/N (%)**	**Odds Ratio 95% CI**	**n/N (%)**	**n/N (%)**	**Odds Ratio 95% CI**	**n/N (%)**	**n/N (%)**	**Odds Ratio 95% CI**
PGA < 2	14/22 (63.6%)	8/24 (33.3%)	4.06 (1.12, 14.72)	26/37 (70.3%)	14/35 (40.0%)	3.42 (1.28, 9.16)	27/31 (87.1%)	13/32 (40.6%)	10.07 (2.78, 36.49)
CRP ≤10 mg/L	13/22 (59.1%)	8/24 (33.3%)	3.88 (1.05, 14.26)	25/37 (67.6%)	9/35 (25.7%)	6.05 (2.14, 17.12)	28/31 (90.3%)	9/32 (28.1%)	22.51 (5.41, 93.62)
SAA ≤10	7/22	2/24	5.06 (0.92,	10/37	4/35	2.94 (0.82,	13/31	5/32	3.73 (1.11,

mg/L	(31.8%)	(8.3%)	27.91)	(27.0%)	(11.4%)	10.53)	(41.9%)	(15.6%)	12.52)

n=number of patients with the response; N=number of patients evaluated for that response in each cohort; CI: Confidence Interval.

*Ilaris-treated patients who up-titrated or discontinued prior to Day 15 and placebo-treated patients who switched over to Ilaris or discontinued prior to Day 15 were classified as non-responders.

14.3 Treatment of SJIA

The efficacy of ILARIS for the treatment of active SJIA was assessed in 2 phase 3 studies (SJIA Study 1 and SJIA Study 2). Patients enrolled were aged 2 to less than 20 years (mean age at baseline: 8.5 years) with a confirmed diagnosis of SJIA at least 2 months before enrollment (mean disease duration at baseline: 3.5 years). Patients had active disease defined as greater than or equal to 2 joints with active arthritis (mean number of active joints at baseline: 15.4), documented spiking, intermittent fever (body temperature greater than 38°C) for at least 1 day within 1 week before study drug administration, and CRP greater than 30 mg/L (normal range less than 10 mg/L) (mean CRP at baseline: 200.5 mg/L). Patients were allowed to continue their stable dose of methotrexate, corticosteroids, and/or NSAIDs without change, except for tapering of the corticosteroid dose as per study design in SJIA Study 2 (see below).

SJIA Study 1 was a randomized, double-blind, placebo-controlled, single-dose 4-week study assessing the short term efficacy of ILARIS in 84 patients randomized to receive a single subcutaneous dose of 4 mg/kg ILARIS or placebo (43 patients received ILARIS and 41 patients received placebo). The primary objective of this study was to demonstrate the superiority of ILARIS versus placebo in the proportion of patients who achieved at least 30% improvement in an adapted pediatric American College of Rheumatology (ACR) response criterion which included both the pediatric ACR core set (ACR30 response) and absence of fever (temperature less than or equal to 38°C in the preceding 7 days) at Day 15.

Pediatric ACR responses are defined by achieving levels of percentage improvement (30%, 50%, and 70%) from baseline in at least 3 of the 6 core outcome variables, with worsening of greater than or equal to 30% in no more than one of the remaining variables. Core outcome variables included a physician global assessment of disease activity, parent or patient global assessment of well-being, number of joints with active arthritis, number of joints with limited range of motion, CRP, and functional ability (Childhood Health Assessment Questionnaire-CHAQ).

Percentages of patients by pediatric ACR response are presented in Table 7.

Table 7 Pediatric ACR Response at Days 15 and 29

	Day 15			**Day 29**		
	ILARIS	**Placebo**	**Weighted Difference[1] (95% CI)[2]**	**ILARIS**	**Placebo**	**Weighted Difference[1] (95% CI)[2]**
	N=43	**N=41**		**N=43**	**N=41**	
ACR30	84%	10%	70% (56%, 84%)	81%	10%	70% (56%, 84%)
ACR50	67%	5%	65% (50%, 80%)	79%	5%	76% (63%, 88%)
ACR70	60%	2%	64% (49%, 79%)	67%	2%	67% (52%, 81%)

[1]Weighted difference is the difference between the ILARIS and placebo response rates, adjusted for the stratification factors (number of active joints, previous response to anakinra, and level of oral corticosteroid use)

[2]CI: confidence interval for the weighted difference

Results for the components of the pediatric ACR core set were consistent with the overall ACR response results, for systemic and arthritic components including the reduction in the total number of active joints and joints with limited range of motion. Among the patients who returned for a Day 15 visit, the mean change in patient pain score (0 to 100 mm visual analogue scale) was -50.0 mm on ILARIS (N=43), as compared to +4.5 mm on placebo (N=25). The mean change in pain score among ILARIS-treated patients was consistent through Day 29. All patients treated with ILARIS had no fever at Day 3 compared to 87% of patients treated with placebo.

SJIA Study 2 was a randomized, double-blind, placebo-controlled, withdrawal study of flare prevention by ILARIS in patients with active SJIA. Flare was defined by worsening of greater than or equal to 30% in at least 3 of the 6 core Pediatric ACR response variables combined with improvement of greater than or equal to 30% in no more than 1 of the 6 variables, or reappearance of fever not due to infection for at least 2 consecutive days. The study consisted of 2 major

parts. One hundred seventy-seven patients were enrolled in the study and received 4 mg/kg ILARIS subcutaneously every 4 weeks in Part I and 100 of these patients continued into Part II to receive either ILARIS 4 mg/kg or placebo subcutaneously every 4 weeks.

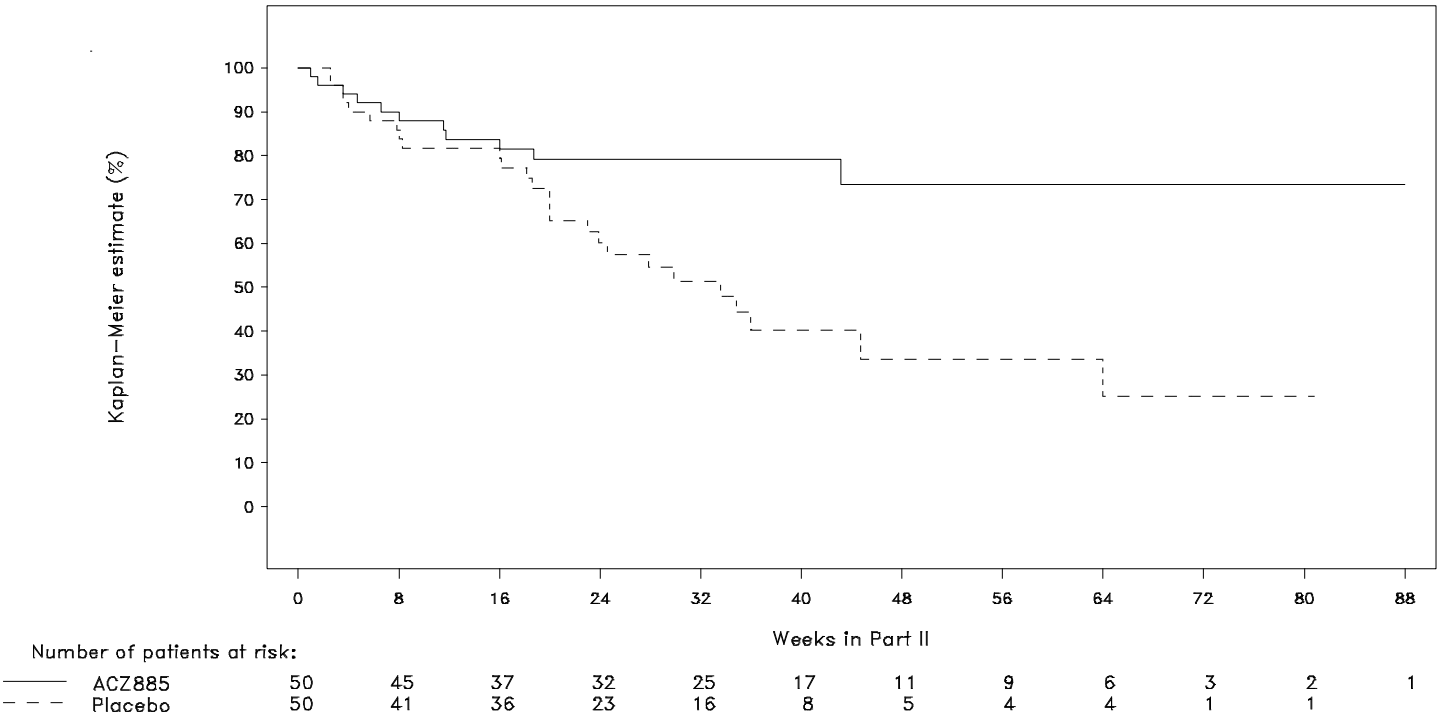
Corticosteroid Dose Tapering

Of the total 128 patients taking corticosteroids who entered the open-label portion of Study 2, 92 attempted corticosteroid tapering. Fifty-seven (62%) of the 92 patients who attempted to taper were able to successfully taper their corticosteroid dose and 42 (46%) discontinued corticosteroids.

Time to Flare

Part II was a randomized withdrawal design to demonstrate that the time to flare was longer with ILARIS than with placebo. Follow-up stopped when 37 events had been observed resulting in patients being followed for different lengths of time. The probability of experiencing a flare over time in Part II was statistically lower for the ILARIS treatment group than for the placebo group (Figure 2). This corresponded to a 64% relative reduction in the risk of flare for patients in the ILARIS group as compared to those in the placebo group (hazard ratio of 0.36; 95% CI: 0.17 to 0.75).

Figure 2. Kaplan-Meier Estimates of the Probability to Stay Flare-Free in Part II of SJIA Study 2 by Treatment



*Very few patients were followed for more than 48 weeks

16 HOW SUPPLIED/STORAGE AND HANDLING

Carton of 1 vial…….NDC 0078-0582-61

Each 150 mg single-dose vial of ILARIS (canakinumab) for Injection contains a sterile, preservative free, white lyophilized powder. After reconstitution with 1 mL of Sterile Water for Injection, the resulting concentration is 150 mg/mL.

Special Precautions for Storage

The unopened vial must be stored refrigerated at 2°C to 8°C (36°F to 46° F). Do not freeze. Store in the original carton to protect from light. Do not use beyond the date stamped on the label. ILARIS does not contain preservatives. Discard any unused portions of ILARIS or waste material in accordance with local requirements.

Keep this and all drugs out of the reach of children.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide)

Patients should be advised of the potential benefits and risks of ILARIS. Physicians should instruct their patients to read the Medication Guide before starting ILARIS therapy.

Drug Administration

Patients should be advised that healthcare providers should perform administration of ILARIS, by the subcutaneous injection route.

Infections

Patients should be cautioned that ILARIS use has been associated with serious infections. Patients should be counseled to contact their healthcare professional immediately if they develop an infection after starting ILARIS. Treatment with ILARIS should be discontinued if a patient develops a serious infection. Patients should be counseled not to take any IL-1 blocking drug, including ILARIS, if they are also taking a drug that blocks TNF such as etanercept, infliximab, or adalimumab. Use of ILARIS with other IL-1 blocking agents, such as rilonacept and anakinra is not recommended. Patients should be cautioned not to receive ILARIS if they have a chronic or active infection, including HIV, Hepatitis B or Hepatitis C.

Vaccinations

Prior to initiation of therapy with ILARIS, physicians should review with adult and pediatric patients their vaccination history relative to current medical guidelines for vaccine use, including taking into account the potential of increased risk of infection during treatment with ILARIS.

Injection-site Reactions

Physicians should explain to patients that a very small number of patients in the clinical trials experienced a reaction at the subcutaneous injection site. Injection-site reactions may include pain, erythema, swelling, pruritus, bruising, mass, inflammation, dermatitis, edema, urticaria, vesicles, warmth, and hemorrhage. Healthcare providers should be cautioned to avoid injecting into an area that is already swollen or red. Any persistent reaction should be brought to the attention of the prescribing physician.

Hypersensitivity

Patients should be counseled to contact their healthcare provider immediately if they develop signs of allergic reaction such as difficulty breathing or swallowing, nausea, dizziness, skin rash, itching, hives, palpitations or low blood pressure.

Pregnancy

Advise female patients of the potential risk to a fetus *[see Use in Specific Populations (8.1)]*.

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Medication Guide

ILARIS® (i-LAHR-us)

(canakinumab)

What is the most important information I should know about ILARIS?

ILARIS can cause serious side effects, including:

- **Increased risk of serious infections.** ILARIS can lower the ability of your immune system to fight infections. Your healthcare provider should:
  - test you for tuberculosis (TB) before you receive ILARIS
  - monitor you closely for symptoms of TB during treatment with ILARIS
  - check you for symptoms of any type of infection before, during, and after your treatment with ILARIS

Tell your healthcare provider right away if you have any symptoms of an infection such as fever, sweats or chills, cough, flu-like symptoms, weight loss, shortness of breath, blood in your phlegm, sores on your body, warm or painful areas on your body, diarrhea or stomach pain, or feeling very tired.

See "What are possible side effects of ILARIS?" for more information about side effects.

What is ILARIS?

ILARIS is a prescription medicine injected by your healthcare provider just below the skin (subcutaneous) used to treat:

- The following Periodic Fever Syndromes
  - Adults and children 4 years of age and older who have auto-inflammatory diseases called Cryopyrin-Associated Periodic Syndromes (CAPS), including:
    - Familial Cold Auto-inflammatory Syndrome (FCAS)
    - Muckle-Wells Syndrome (MWS)
  - Adults and children who have an auto-inflammatory disease called Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS)
  - Adults and children who have an auto-inflammatory disease called Hyperimmunoglobulin D Syndrome (HIDS)/(also known as Mevalonate Kinase Deficiency (MKD).
  - Adults and children who have an auto-inflammatory disease called Familial Mediterranean Fever (FMF).
- Systemic Juvenile Idiopathic Arthritis (SJIA) in children 2 years of age and older.

It is not known if ILARIS is safe and effective when used to treat SJIA in children under 2 years of age or when used to treat CAPS in children under 4 years of age.

Who should not receive ILARIS?

- Do not receive ILARIS if you are allergic to canakinumab or any of the ingredients in ILARIS. See the end of this Medication Guide for a complete list of ingredients in ILARIS.

Before you receive ILARIS, tell your healthcare provider about all your medical conditions, including if you:

- think you have or are being treated for an active infection
- have symptoms of an infection
- have a history of infections that keep coming back
- have a history of low white blood cells
- have or have had HIV, Hepatitis B, or Hepatitis C
- are scheduled to receive any immunizations (vaccines). You should not get 'live vaccines' if you are receiving ILARIS.
- are pregnant or planning to become pregnant. It is not known if ILARIS will harm your unborn baby. Tell your healthcare provider right away if you become pregnant while receiving ILARIS.
- are breastfeeding or planning to breastfeed. It is not known if ILARIS passes into your breast milk. You and your healthcare provider should decide if you will receive ILARIS or breastfeed. You should not do both.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Especially tell your healthcare provider if you take:

- Medicines that affect your immune system
- Medicines called IL-1 blocking agents such as Kineret® (anakinra), Arcalyst® (rilonacept)
- Medicines called Tumor Necrosis Factor (TNF) inhibitors such as Enbrel® (etanercept), Humira® (adalimumab), Remicade® (infliximab), Simponi® (golimumab), or Cimzia® (certolizumab pegol)
- Medicines that effect enzyme metabolism

Ask your healthcare provider for a list of these medicines if you are not sure.

How should I receive ILARIS?

- ILARIS is given by your healthcare provider every 8 weeks for CAPS and every 4 weeks for TRAPS, HIDS/MKD, FMF, and SJIA.

What are the possible side effects of ILARIS?

ILARIS can cause serious side effects, including:

- See **"What is the most important information I should know about ILARIS?"**
- **decreased ability of your body to fight infections (immunosuppression).** For people treated with medicines that cause immunosuppression like ILARIS, the chances of getting cancer may increase.
- **allergic reactions.** Allergic reactions can happen while you are receiving ILARIS. Call your healthcare provider right away if you have any of these symptoms of an allergic reaction:
    - rash
    - itching and hives
    - difficulty breathing or swallowing
    - dizziness or feeling faint
- **risk of infection with live vaccines.** You should not get live vaccines if you are receiving ILARIS. Tell your healthcare provider if you are scheduled to receive any vaccines.

The most common side effects of ILARIS include:

When ILARIS is used for the treatment of CAPS:

- cold symptoms
- diarrhea
- flu (influenza)
- runny nose
- headache
- cough
- body aches
- nausea, vomiting, and diarrhea (gastroenteritis)
- feeling like you are spinning (vertigo)
- weight gain
- injection site reactions (such as redness, swelling, warmth, or itching)
- nausea

When ILARIS is used for the treatment of TRAPS, HIDS/MKD, and FMF:

- cold symptoms
- Upper respiratory tract infection
- runny nose
- sore throat
- nausea, vomiting, and diarrhea (gastroenteritis)
- Injection site reactions (such as redness, swelling, warmth, or itching)

When ILARIS is used for the treatment of SJIA:

- cold symptoms
- upper respiratory tract infection
- runny nose
- sore throat
- nausea, vomiting, and diarrhea (gastroenteritis)
- stomach pain

- pneumonia
- urinary tract infection
- injection site reactions

Tell your healthcare provider about any side effect that bothers you or does not go away. These are not all the possible side effects of ILARIS. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of ILARIS.

Medicines are sometimes prescribed for purposes other than those listed in this Medication Guide. Do not use ILARIS for a condition for which it was not prescribed.

You can ask your healthcare provider or pharmacist for information about ILARIS that was written for health professionals.

What are the ingredients in ILARIS?

Active ingredient: canakinumab

Inactive ingredients:

L-histidine, L-histidine HCl monohydrate, polysorbate 80, sterile water for injection, sucrose

What are Periodic Fever Syndromes?

Periodic Fever Syndromes is the name for several different autoinflammatory diseases, including CAPS, TRAPS, HIDS/MKD, and FMF. People with these diseases cannot keep certain chemicals made by their body (interleukin-1 beta, also called IL-1β) at the correct level. All these diseases have symptoms that often come and go, with irritated body parts (inflammation) and elevated body temperature (fever). These conditions have a dysregulation of IL-1β production and share similar clinical features of recurrent episodes of inflammation and fever such as rash, headache, pain (mostly in the joints, belly, eyes, muscles), fatigue, inflammation of other organs such as heart, lungs, spleen, and brain.

What is SJIA?

SJIA is an autoinflammatory disorder which can be caused by having too much or being too sensitive to certain proteins, including interleukin-1β (IL-1β), and can lead to symptoms such as fever, rash, headache, feeling very tired (fatigue), or painful joints and muscles.

What is Macrophage Activation Syndrome (MAS)?

MAS is a syndrome associated with SJIA and some other autoinflammatory diseases like HIDS/MKD that can lead to death. Tell your healthcare provider right away if your SJIA symptoms get worse or if you have any of these symptoms of an infection:

- a fever lasting longer than 3 days
- a cough that does not go away
- redness in one part of your body
- warm feeling or swelling of your skin

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Distributed by:
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East Hanover
New Jersey 07936

For more information about ILARIS, call 1-877-452-7471 or visit www.ILARIS.com.

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T2016-79/T2016-80

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Revised: September 2016/September 2016

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Ilaris 150 mg powder for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains 150 mg of canakinumab*.

After reconstitution, each ml of solution contains 150 mg canakinumab.

* fully human monoclonal antibody produced in mouse hybridoma Sp2/0 cells by recombinant DNA technology

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection.

The powder is white.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Cryopyrin-Associated Periodic Syndromes
Ilaris is indicated for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS) in adults, adolescents and children aged 2 years and older with body weight of 7.5 kg or above, including:
- Muckle-Wells Syndrome (MWS),
- Neonatal-Onset Multisystem Inflammatory Disease (NOMID) / Chronic Infantile Neurological, Cutaneous, Articular Syndrome (CINCA),
- Severe forms of Familial Cold Autoinflammatory Syndrome (FCAS) / Familial Cold Urticaria (FCU) presenting with signs and symptoms beyond cold-induced urticarial skin rash.

Still's Disease
Ilaris is indicated for the treatment of active Still's disease including Adult-Onset Still's Disease (AOSD) and Systemic Juvenile Idiopathic Arthritis (SJIA) in patients aged 2 years and older who have responded inadequately to previous therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids. Ilaris can be given as monotherapy or in combination with methotrexate.

Gouty arthritis
Ilaris is indicated for the symptomatic treatment of adult patients with frequent gouty arthritis attacks (at least 3 attacks in the previous 12 months) in whom non-steroidal anti-inflammatory drugs (NSAIDs) and colchicine are contraindicated, are not tolerated, or do not provide an adequate response, and in whom repeated courses of corticosteroids are not appropriate (see section 5.1).

4.2 Posology and method of administration

For CAPS and Still's disease, the treatment should be initiated and supervised by a specialist physician experienced in the diagnosis and treatment of the relevant indication.

For gouty arthritis, the physician should be experienced in the use of biologics and Ilaris should be administered by a healthcare professional.

After proper training in the correct injection technique, patients or their caregivers may inject Ilaris if the physician determines that it is appropriate and with medical follow-up as necessary (see section 6.6).

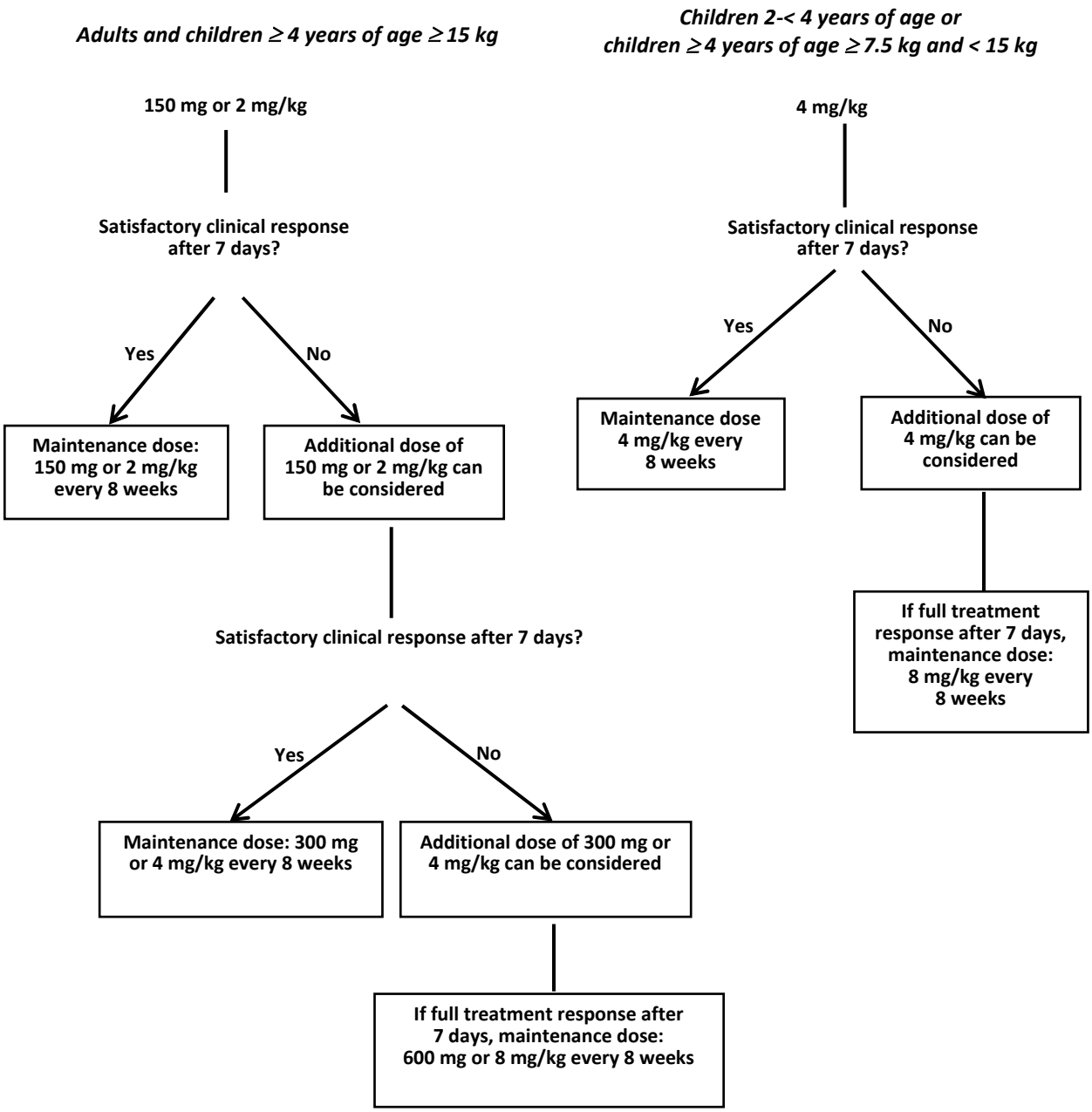
Posology
CAPS: Adults, adolescents and children aged 2 years and older
The recommended starting dose of Ilaris for CAPS patients is:
Adults, adolescents and children ≥ 4 years of age:
– 150 mg for patients with body weight > 40 kg
– 2 mg/kg for patients with body weight ≥ 15 kg and ≤ 40 kg
– 4 mg/kg for patients with body weight ≥ 7.5 kg and < 15 kg
Children 2 to < 4 years of age:
– 4 mg/kg for patients with body weight ≥ 7.5 kg

This is administered every eight weeks as a single dose via subcutaneous injection.

For patients with a starting dose of 150 mg or 2 mg/kg, if a satisfactory clinical response (resolution of rash and other generalised inflammatory symptoms) has not been achieved 7 days after treatment start, a second dose of Ilaris at 150 mg or 2 mg/kg can be considered. If a full treatment response is subsequently achieved, the intensified dosing regimen of 300 mg or 4 mg/kg every 8 weeks should be maintained. If a satisfactory clinical response has not been achieved 7 days after this increased dose, a third dose of Ilaris at 300 mg or 4 mg/kg can be considered. If a full treatment response is subsequently achieved, maintaining the intensified dosing regimen of 600 mg or 8 mg/kg every 8 weeks should be considered, based on individual clinical judgement.

For patients with a starting dose of 4 mg/kg, if a satisfactory clinical response has not been achieved 7 days after treatment start, a second dose of Ilaris 4 mg/kg can be considered. If a full treatment response is subsequently achieved, maintaining the intensified dosing regimen of 8 mg/kg every 8 weeks should be considered, based on individual clinical judgement.

Clinical experience with dosing at intervals of less than 4 weeks or at doses above 600 mg or 8 mg/kg is limited.



Still's Disease (AOSD and SJIA)

The recommended dose of Ilaris for patients with Still's disease (AOSD and SJIA) with body weight ≥ 7.5 kg is 4 mg/kg (up to a maximum of 300 mg) administered every four weeks via subcutaneous injection. Continued treatment with Ilaris in patients without clinical improvement should be reconsidered by the treating physician.

Gouty arthritis

Management of hyperuricaemia with appropriate urate lowering therapy (ULT) should be instituted or optimised. Ilaris should be used as an on-demand therapy to treat gouty arthritis attacks.

The recommended dose of Ilaris for adult patients with gouty arthritis is 150 mg administered subcutaneously as a single dose during an attack. For maximum effect, Ilaris should be administered as soon as possible after the onset of a gouty arthritis attack.

Patients who do not respond to initial treatment should not be re-treated with Ilaris. In patients who respond and require re-treatment, there should be an interval of at least 12 weeks before a new dose of Ilaris may be administered (see section 5.2).

Special populations
Paediatric population
CAPS
The safety and efficacy of Ilaris in CAPS patients under 2 years of age have not been established. Currently available data are described in sections 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

SJIA
The safety and efficacy of Ilaris in SJIA patients under 2 years of age have not been established.

Gouty arthritis
There is no relevant use of Ilaris in the paediatric population in the indication gouty arthritis.

Elderly
No dose adjustment is required.

Hepatic impairment
Ilaris has not been studied in patients with hepatic impairment.

Renal impairment
No dose adjustment is needed in patients with renal impairment. However, clinical experience in such patients is limited.

Method of Administration
Ilaris is to be administered via subcutaneous injection. For instructions on use and handling of the reconstituted solution, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Active, severe infections (see section 4.4).

4.4 Special warnings and precautions for use

Infections
Ilaris is associated with an increased incidence of serious infections. Therefore patients should be monitored carefully for signs and symptoms of infections during and after treatment with Ilaris. Physicians should exercise caution when administering Ilaris to patients with infections, a history of recurring infections, or underlying conditions which may predispose them to infections.

Treatment of CAPS and Still's Disease (AOSD and SJIA)
Ilaris should not be initiated or continued in patients during an active infection requiring medical intervention.

Treatment of gouty arthritis
Ilaris should not be administered during an active infection.

Concomitant use of Ilaris with tumour necrosis factor (TNF) inhibitors is not recommended because this may increase the risk of serious infections (see section 4.5).

Isolated cases of unusual or opportunistic infections (including aspergillosis, atypical mycobacterial infections, herpes zoster) have been reported during Ilaris treatment. The causal relationship of Ilaris to these events cannot be excluded.

In approximately 12% of CAPS patients tested with a PPD (purified protein derivative) skin test in clinical trials, follow-up testing yielded a positive test result while treated with Ilaris without clinical evidence of a latent or active tuberculosis infection.

It is unknown whether the use of interleukin-1 (IL-1) inhibitors such as Ilaris increases the risk of reactivation of tuberculosis. Before initiation of therapy, all patients must be evaluated for both active and latent tuberculosis infection. Particularly in adult patients, this evaluation should include a detailed medical history. Appropriate screening tests (e.g. tuberculin skin test, interferon gamma release assay or chest X-ray) should be performed in all patients (local recommendations may apply). Patients must be monitored closely for signs and symptoms of tuberculosis during and after treatment with Ilaris. All patients should be instructed to seek medical advice if signs or symptoms suggestive of tuberculosis (e.g. persistent cough, weight loss, subfebrile temperature) appear during Ilaris therapy. In the event of conversion from a negative to a positive PPD test, especially in high-risk patients, alternative means of screening for a tuberculosis infection should be considered.

Neutropenia and leukopenia
Neutropenia (absolute neutrophil count [ANC] < 1.5 x 10^9/l) and leukopenia have been observed with medicinal products that inhibit IL-1, including Ilaris. Treatment with Ilaris should not be initiated in patients with neutropenia or leukopenia. It is recommended that white blood cell (WBC) counts including neutrophil counts be assessed prior to initiating treatment and again after 1 to 2 months. For chronic or repeated therapies, it is also recommended to assess WBC counts periodically during treatment. If a patient becomes neutropenic or leukopenic, the WBC counts should be monitored closely and treatment discontinuation should be considered.

Malignancies
Malignancy events have been reported in patients treated with Ilaris. The risk for the development of malignancies with anti-interleukin (IL)-1 therapy is unknown.

Hypersensitivity reactions
Hypersensitivity reactions with Ilaris therapy have been reported. The majority of these events were mild in severity. During clinical development of Ilaris in over 2,300 patients, no anaphylactoid or anaphylactic reactions were reported. However, the risk of severe hypersensitivity reactions, which is not uncommon for injectable proteins, cannot be excluded (see section 4.3).

Hepatic function
Transient and asymptomatic cases of elevations of serum transaminases or bilirubin have been reported in clinical trials (see section 4.8).

Vaccinations
No data are available on the risk of secondary transmission of infection by live (attenuated) vaccines in patients receiving Ilaris. Therefore, live vaccines should not be given concurrently with Ilaris unless the benefits clearly outweigh the risks (see section 4.5).

Prior to initiation of Ilaris therapy it is recommended that adult and paediatric patients receive all vaccinations, as appropriate, including pneumococcal vaccine and inactivated influenza vaccine (see section 4.5).

Mutation in NLRP3 gene in CAPS patients
Clinical experience in CAPS patients without a confirmed mutation in the NLRP3 gene is limited.

Macrophage activation syndrome in patients with Still's Disease
Macrophage activation syndrome (MAS) is a known, life-threatening disorder that may develop in patients with rheumatic conditions, in particular Still's disease. If MAS occurs, or is suspected, evaluation and treatment should be started as early as possible. Physicians should be attentive to symptoms of infection or worsening of Still's disease, as these are known triggers for MAS. Based on clinical trial experience, Ilaris does not appear to increase the incidence of MAS in SJIA patients, but no definitive conclusion can be made.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions between Ilaris and other medicinal products have not been investigated in formal studies.

An increased incidence of serious infections has been associated with administration of another IL-1 blocker in combination with TNF inhibitors. Use of Ilaris with TNF inhibitors is not recommended because this may increase the risk of serious infections.

The expression of hepatic CYP450 enzymes may be suppressed by the cytokines that stimulate chronic inflammation, such as interleukin-1 beta (IL-1 beta). Thus, CYP450 expression may be reversed when potent cytokine inhibitory therapy, such as canakinumab, is introduced. This is clinically relevant for CYP450 substrates with a narrow therapeutic index where the dose is individually adjusted. On initiation of canakinumab in patients being treated with this type of medicinal product, therapeutic monitoring of the effect or of the active substance concentration should be performed and the individual dose of the medicinal product adjusted as necessary.

No data are available on either the effects of live vaccination or the secondary transmission of infection by live vaccines in patients receiving Ilaris. Therefore, live vaccines should not be given concurrently with Ilaris unless the benefits clearly outweigh the risks. Should vaccination with live vaccines be indicated after initiation of Ilaris treatment, the recommendation is to wait for at least 3 months after the last Ilaris injection and before the next one (see section 4.4).

The results of a study in healthy adult subjects demonstrated that a single dose of Ilaris 300 mg did not affect the induction and persistence of antibody responses after vaccination with influenza or glycosylated protein based meningococcus vaccines.

The results of a 56-week, open label study in CAPS patients aged 4 years and younger demonstrated that all patients who received non-live, standard of care childhood vaccinations developed protective antibody levels.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females
Women should use effective contraceptives during treatment with Ilaris and for up to 3 months after the last dose.

Pregnancy
There is a limited amount of data from the use of canakinumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). The risk for the foetus/mother is unknown. Women who are pregnant or who desire to become pregnant should therefore only be treated after a thorough benefit-risk evaluation.

Animal studies indicate that canakinumab crosses the placenta and is detectable in the foetus. No human data are available, but as canakinumab is an immunoglobulin of the G class (IgG1), human transplacental transfer is expected. The clinical impact of this is unknown. However, administration of live vaccines to newborn infants exposed to canakinumab *in utero* is not recommended for 16 weeks following the mother's last dose of Ilaris before childbirth. Women who received canakinumab during pregnancy should be instructed to inform the baby's healthcare professional before any vaccinations are given to their newborn infant.

Breast-feeding
It is unknown whether canakinumab is excreted in human milk. The decision whether to breast-feed during Ilaris therapy should therefore only be taken after a thorough benefit-risk evaluation.

Animal studies have shown that a murine anti-murine IL-1 beta antibody had no undesirable effects on development in nursing mouse pups and that the antibody was transferred to them (see section 5.3).

Fertility
Formal studies of the potential effect of Ilaris on human fertility have not been conducted. Canakinumab had no effect on male fertility parameters in marmosets (*C. jacchus*). A murine anti-murine IL-1 beta antibody had no undesirable effects on fertility in male or female mice (see section 5.3).

4.7 Effects on ability to drive and use machines

Ilaris has minor influence on the ability to drive and use machines. Treatment with Ilaris may result in dizziness/vertigo or asthenia (see section 4.8). Patients who experience such symptoms during Ilaris treatment should wait for this to resolve completely before driving or operating machines.

4.8 Undesirable effects

Summary of the safety profile
Over 2,400 subjects including approximately 380 children (aged 2 to 17 years) have been treated with Ilaris in interventional studies in patients with CAPS, SJIA, gouty arthritis or other IL-1 beta mediated diseases, and healthy volunteers. Serious infections have been observed. The most frequent adverse drug reactions were infections predominantly of the upper respiratory tract. The majority of the events were mild to moderate. No impact on the type or frequency of adverse drug reactions was seen with longer-term treatment.

Hypersensitivity reactions have been reported in patients treated with Ilaris (see sections 4.3 and 4.4).

Opportunistic infections have been reported in patients treated with Ilaris (see section 4.4).

CAPS
A total of 211 adult and paediatric CAPS patients (including FCAS/FCU, MWS, and NOMID/CINCA) have received Ilaris in clinical trials. The safety of Ilaris compared with placebo was investigated in a pivotal phase III trial that consisted of an 8-week, open-label period (Part I), a 24-week, randomised, double-blind and placebo-controlled withdrawal period (Part II), and a 16-week open label period on Ilaris (Part III). All patients were treated with Ilaris 150 mg subcutaneous or 2 mg/kg if body weight was ≥ 15 kg and ≤ 40 kg.

Still's Disease
A total of 324 SJIA patients aged 2 to < 20 years have received Ilaris in clinical trials, including 293 patients aged 2 to < 16 years old, 21 patients aged 16 to < 18 years old and 10 patients aged 18 to < 20 years old. The safety of Ilaris compared to placebo was investigated in two pivotal Phase III studies (see section 5.1).

Gouty arthritis
More than 700 patients with gouty arthritis have been treated with Ilaris at doses from 10 mg to 300 mg in randomised, double-blind and active-controlled clinical trials of up to 24 weeks' duration. More than 250 patients have been treated with the recommended dose of 150 mg in Phase II and III trials (see section 5.1).

Tabulated list of adverse reactions
Adverse reactions are listed according to MedDRA system organ class. Within each system organ class, the adverse reactions are ranked by frequency category with the most common first. Frequency categories are defined using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1 Tabulated list of adverse reactions in CAPS, SJIA and gouty arthritis

MedDRA System Organ Class	CAPS	SJIA	Gouty arthritis
Infections and infestations			
Very Common	Nasopharyngitis	Pneumonia Gastroenteritis Urinary tract infection Viral infection Sinusitis Rhinitis Pharyngitis Tonsilitis Nasopharyngitis Upper respiratory tract infection	Pneumonia Bronchitis Gastroenteritis Urinary tract infection Influenza Cellulitis Sinusitis Ear infection Pharyngitis Nasopharyngitis Upper respiratory tract infection
Common	Urinary tract infection Upper respiratory tract infection Viral infection		
Nervous system disorders			
Common	Dizziness/vertigo		Dizziness/vertigo
Gastrointestinal disorders			
Very common		Abdominal pain (upper)	
Uncommon			Gastro-oesophageal reflux disease
Skin and subcutaneous tissue disorders			
Very common	Injection site reaction	Injection site reaction	
Common			Injection site reaction
Musculoskeletal and connective tissue disorders			
Very common		Arthralgia	
Common		Musculoskeletal pain	Back pain
General disorders and administration site conditions			
Common			Fatigue/asthenia
Investigations			
Very common		Creatinine renal clearance decreased * Proteinuria # Leukopenia	
Common		Neutropenia	
* based on estimated creatinine clearance, most were transient # most represented transient trace to 1+ positive urinary protein by dipstick			

In a subset of young adult SJIA patients aged 16 to 20 years (n=31), the safety profile of Ilaris was consistent with what was observed in SJIA patients less than 16 years of age. The safety profile in AOSD patients is expected to be similar to SJIA patients based on literature reports.

Description of selected adverse reactions

Long-term data and laboratory abnormalities in CAPS patients

During clinical trials with Ilaris in CAPS patients mean values for haemoglobin increased and those for white blood cell, neutrophils and platelets decreased.

Elevations of transaminases have been observed rarely in CAPS patients.

Asymptomatic and mild elevations of serum bilirubin have been observed in CAPS patients treated with Ilaris without concomitant elevations of transaminases.

In the long-term, open-label studies with dose escalation, events of infections (gastroenteritis, respiratory tract infection, upper respiratory tract infection), vomiting and dizziness were more frequently reported in the 600 mg or 8 mg/kg dose group than in other dose groups.

Laboratory abnormalities in SJIA patients
Haematology
In the overall SJIA program, transient decreased white blood cell (WBC) counts ≤ 0.8 x LLN were reported in 33 patients (16.5%).

In the overall SJIA program, transient decreases in absolute neutrophil count (ANC) to less than 1 x 10^9/l were reported in 12 patients (6.0%).

In the overall SJIA program, transient decreases in platelet counts (< LLN) were observed in 19 patients (9.5%).

ALT/AST
In the overall SJIA program, high ALT and/or AST > 3 x upper limit of normal (ULN) were reported in 19 patients (9.5%).

Laboratory abnormalities in gouty arthritis patients
Haematology
Decreased white blood cell counts (WBC) ≤ 0.8 x lower limit of normal (LLN) were reported in 6.7% of patients treated with Ilaris compared to 1.4% treated with triamcinolone acetonide. Decreases in absolute neutrophil counts (ANC) to less than 1 x 10^9/l were reported in 2% of patients in the comparative trials. Isolated cases of ANC counts < 0.5 x 10^9/l were also observed (see section 4.4).

Mild (< LLN and > 75 x 10^9/l) and transient decreases in platelet counts were observed at a higher incidence (12.7%) with Ilaris in the active-controlled clinical studies versus the comparator (7.7%) in gouty arthritis patients.

Uric acid
Increases in uric acid level (0.7 mg/dl at 12 weeks and 0.5 mg/dl at 24 weeks) were observed after Ilaris treatment in comparative trials in gouty arthritis. In another study, among patients who were starting on ULT, increases in uric acid were not observed. Uric acid increases were not observed in clinical trials in non-gouty arthritis populations (see section 5.1).

ALT/AST
Mean and median increases in alanine transaminase (ALT) of 3.0 U/l and 2.0 U/l, respectively, and in aspartate transaminase (AST) of 2.7 U/l and 2.0 U/l, respectively, from baseline to end of study were seen in the Ilaris-treated groups versus the triamcinolone acetonide-treated group(s), however the incidence of clinically significant changes (≥ 3 x the upper limit of normal) was greater for patients treated with triamcinolone acetonide (2.5% for both AST and ALT) compared with Ilaris-treated patients (1.6% for ALT and 0.8% for AST).

Triglycerides
In active-controlled gouty arthritis trials, there was a mean increase in triglycerides of 33.5 mg/dl in Ilaris-treated patients compared with a modest decrease of -3.1 mg/dl with triamcinolone acetonide. The incidence of patients with triglyceride elevations > 5 x upper limit of normal (ULN) was 2.4% with Ilaris and 0.7% with triamcinolone acetonide. The clinical significance of this observation is unknown.

Paediatric population
There were 80 paediatric CAPS patients (2-17 years of age) included in the studies. Overall, there were no clinically meaningful differences in the safety and tolerability profile of Ilaris in paediatric patients compared to the overall CAPS population (comprised of adult and paediatric patients, N=211), including the overall frequency and severity of infectious episodes. Infections of the upper respiratory tract were the most frequently reported infection events.

Additionally, 6 paediatric patients under the age of 2 years were evaluated in a small open-label clinical study. The safety profile of Ilaris appeared similar to that in patients aged 2 years and above.

Elderly population
There is no significant difference in safety profile observed in patients ≥ 65 years of age.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Reported experience with overdose is limited. In early clinical trials, patients and healthy volunteers received doses as high as 10 mg/kg, administered intravenously or subcutaneously, without evidence of acute toxicity.

In case of overdose, it is recommended for the patient to be monitored for any signs or symptoms of adverse reactions, and appropriate symptomatic treatment instituted immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, interleukin inhibitors, ATC code: L04AC08

Mechanism of action
Canakinumab is a fully human monoclonal anti-human interleukin-1 beta (IL-1 beta) antibody of the IgG1/κ isotype. Canakinumab binds with high affinity specifically to human IL-1 beta and neutralises the biological activity of human IL-1 beta by blocking its interaction with IL-1 receptors, thereby preventing IL-1 beta-induced gene activation and the production of inflammatory mediators.

Pharmacodynamic effects
CAPS
In clinical studies, CAPS patients who have uncontrolled over-production of IL-1 beta show a rapid response to therapy with canakinumab, i.e. laboratory parameters such as high C-reactive protein (CRP) and serum amyloid A (SAA), high neutrophil and platelet counts, and leukocytosis rapidly returned to normal.

Still's Disease (AOSD and SJIA)
Adult-Onset Still's Disease and Systemic Juvenile Idiopathic Arthritis are severe autoinflammatory diseases, driven by innate immunity by means of pro-inflammatory cytokines, a key one being IL-1-beta.

Common features of AOSD and SJIA include fever, rash, hepatosplenomegaly, lymphadenopathy, polyserositis and arthritis. Treatment with canakinumab resulted in a rapid and sustained improvement of both the articular and the systemic features of SJIA with significant reduction of the number of

inflamed joints, prompt resolution of fever and reduction of acute phase reactants in the majority of patients (see Clinical efficacy and safety).

Gouty arthritis
A gouty arthritis attack is caused by urate (monosodium urate monohydrate) crystals in the joint and surrounding tissue, which trigger resident macrophages to produce IL-1 beta via the "NALP3 inflammasome" complex. Activation of macrophages and concomitant over-production of IL-1 beta results in an acute painful inflammatory response. Other activators of the innate immune system, such as endogenous agonists of toll-like receptors, may contribute to the transcriptional activation of the IL-1 beta gene, initiating a gouty arthritis attack. Following canakinumab treatment, the inflammatory markers CRP or SAA and signs of acute inflammation (e.g. pain, swelling, redness) in the affected joint subside rapidly.

Clinical efficacy and safety
CAPS
The efficacy and safety of Ilaris have been demonstrated in patients with varying degrees of disease severity and different CAPS phenotypes (including FCAS/FCU, MWS, and NOMID/CINCA). Only patients with confirmed NLRP3 mutation were included in the pivotal study.

In the Phase I/II study, treatment with Ilaris had a rapid onset of action, with disappearance or clinically significant improvement of symptoms within one day after dosing. Laboratory parameters such as high CRP and SAA, high neutrophils and platelet counts normalised rapidly within days of Ilaris injection.

The pivotal study consisted of a 48-week three-part multicentre study, i.e. an 8-week open-label period (Part I), a 24-week randomised, double-blind, placebo-controlled withdrawal period (Part II), followed by a 16-week open-label period (Part III). The aim of the study was to assess efficacy, safety, and tolerability of Ilaris (150 mg or 2 mg/kg every 8 weeks) in patients with CAPS.

- Part I: A complete clinical and biomarker response to Ilaris (defined as composite of physician's global assessment on autoinflammatory and on skin disease ≤ minimal and CRP or SAA values < 10 mg/litre) was observed in 97% of patients and appeared within 7 days of initiation of treatment. Significant improvements were seen in physician's clinical assessment of autoinflammatory disease activity: global assessment of autoinflammatory disease activity, assessment of skin disease (urticarial skin rash), arthralgia, myalgia, headache/migraine, conjunctivitis, fatigue/malaise, assessment of other related symptoms, and patient's assessment of symptoms.

- Part II: In the withdrawal period of the pivotal study, the primary endpoint was defined as the proportion of patients with a disease relapse/flare: none (0%) of the patients randomised to Ilaris flared, compared with 81% of the patients randomised to placebo.

- Part III: Patients treated with placebo in Part II who flared regained and maintained clinical and serological response following entry into the open-label Ilaris extension.

Table 2 Tabulated summary of efficacy in Phase III trial, pivotal placebo-controlled withdrawal period (Part II)

Phase III trial, pivotal placebo-controlled withdrawal period (Part II)			
	Ilaris N=15 n(%)	Placebo N=16 n(%)	p-value
Primary endpoint (flare)			
Proportion of patients with disease flare in Part II	0 (0%)	13 (81%)	< 0.001
Inflammatory markers*			
C-reactive protein, mg/l	1.10 (0.40)	19.93 (10.50)	< 0.001
Serum amyloid A, mg/l	2.27 (-0.20)	71.09 (14.35)	0.002
* mean (median) change from beginning of Part II			

Two open-label, uncontrolled, long-term phase III studies were performed. One was a safety, tolerability, and efficacy study of canakinumab in patients with CAPS. The total treatment duration ranged from 6 months to 2 years. The other was an open-label study with canakinumab to evaluate the efficacy and safety in Japanese CAPS patients for 24 weeks, with an extension phase up to 48 weeks. The primary objective was to assess the proportion of patients who were free of relapse at week 24, including those patients whose dose was increased.

In the pooled efficacy analysis for these two studies, 65.6% of patients who had not previously been treated with canakinumab achieved complete response at 150 mg or 2 mg/kg, while 85.2% of patients achieved complete response at any dose. Of the patients treated with 600 mg or 8 mg/kg (or even higher), 43.8% achieved complete response. Fewer patients aged 2 to < 4 years achieved complete response (57.1%) than older paediatric and adult patients. Of the patients who had achieved a complete response, 89.3% maintained response without relapsing.

Experience from individual patients who achieved a complete response following dose escalation to 600 mg (8 mg/kg) every 8 weeks suggests that a higher dose may be beneficial in patients not achieving complete response or not maintaining complete response with the recommended doses (150 mg or 2 mg/kg for patients ≥ 15 kg and ≤ 40 kg). An increased dose was administered more frequently to patients aged 2 to < 4 years and to patients with NOMID/CINCA symptoms compared with FCAS or MWS.

Paediatric population
The CAPS trials with Ilaris included a total of 80 paediatric patients with an age range from 2 to 17 years (approximately half of them treated on an mg/kg basis). Overall, there were no clinically meaningful differences in the efficacy, safety and tolerability profile of Ilaris in paediatric patients compared to the overall CAPS population. The majority of paediatric patients achieved improvement in clinical symptoms and objective markers of inflammation (e.g. SAA and CRP).

A 56-week, open-label study was conducted to assess the efficacy, safety and tolerability of Ilaris in paediatric CAPS patients ≤4 years of age. Seventeen patients (including 6 patients under the age of 2 years) were evaluated, using weight-based starting doses of 2-8 mg/kg. The study also evaluated the effect of canakinumab on the development of antibodies to standard childhood vaccines. No differences in safety or efficacy were observed in patients under the age of 2 years compared with patients aged 2 years and above. All patients who received non-live, standard of care childhood vaccinations (N=7) developed protective antibody levels.

Still's Disease
SJIA
The efficacy of Ilaris for the treatment of active SJIA was assessed in two pivotal studies (G2305 and G2301). Patients enrolled were aged 2 to < 20 years (mean age of 8.5 years and mean disease duration

of 3.5 years at baseline) and had active disease defined as ≥ 2 joints with active arthritis, fever and elevated CRP.

Study G2305
Study G2305 was a randomised, double-blind, placebo-controlled, 4-week study assessing the short-term efficacy of Ilaris in 84 patients randomised to receive a single dose of 4 mg/kg (up to 300 mg) Ilaris or placebo. The primary objective was the proportion of patients at day 15 who achieved a minimum 30% improvement in the paediatric American College of Rheumatology (ACR) response criterion adapted to include absence of fever. Ilaris treatment improved all paediatric ACR response scores as compared to placebo at days 15 and 29 (Table 3).

Table 3 Paediatric ACR response and disease status at days 15 and 29

	Day 15		Day 29	
	Ilaris N=43	Placebo N=41	Ilaris N=43	Placebo N=41
ACR30	84%	10%	81%	10%
ACR50	67%	5%	79%	5%
ACR70	61%	2%	67%	2%
ACR90	42%	0%	47%	2%
ACR100	33%	0%	33%	2%
Inactive disease	33%	0%	30%	0%
Treatment difference for all ACR scores was significant ($p \leq 0.0001$)				

Results for the components of the adapted paediatric ACR which included systemic and arthritic components, were consistent with the overall ACR response results. At day 15, the median change from baseline in the number of joints with active arthritis and limited range of motion were -67% and -73% for Ilaris (N=43), respectively, compared to a median change of 0% and 0% for placebo (N=41). The mean change in patient pain score (0-100 mm visual analogue scale) at day 15 was -50.0 mm for Ilaris (N=43), as compared to +4.5 mm for placebo (N=25). The mean change in pain score among Ilaris treated patients was consistent at day 29.

Study G2301
Study G2301 was a randomised, double-blind, placebo-controlled withdrawal study of flare prevention by Ilaris. The study consisted of two parts with two independent primary endpoints (successful steroid taper and time to flare). In part I (open label) 177 patients were enrolled and received 4 mg/kg (up to 300 mg) Ilaris administered every 4 weeks for up to 32 weeks. Patients in part II (double-blind) received either Ilaris 4 mg/kg or placebo every 4 weeks until 37 flare events occurred.

Corticosteroid dose tapering:
Of the total 128 patients who entered part I taking corticosteroids, 92 attempted corticosteroid tapering. Fifty-seven (62%) of the 92 patients who attempted to taper were able to successfully taper their corticosteroid dose and 42 (46%) discontinued corticosteroids.

Time to flare:
Patients taking Ilaris in part II had a 64% reduced risk of a flare event as compared to the placebo group (hazard ratio of 0.36; 95% CI: 0.17 to 0.75; p=0.0032). Sixty-three of the 100 patients entering part II, whether assigned to placebo or canakinumab, did not experience a flare over the observation period (up to a maximum of 80 weeks).

Health-related and quality of life outcomes in studies G2305 and G2301
Treatment with Ilaris resulted in clinically relevant improvements in patients' physical function and quality of life. In study G2305, the Childhood Health Assessment Questionnaire Least Squares means improvement was 0.69 for Ilaris vs placebo representing 3.6 times the minimal clinically important difference of 0.19 (p=0.0002). The median improvement from baseline to end of part I of study G2301 was 0.88 (79%). Statistically significant improvements in the Child Health Questionnaire-PF50 scores

were reported for Ilaris vs placebo in study G2305 (physical p=0.0012; psychosocial well-being p=0.0017).

Pooled Efficacy Analysis
Data from the first 12 weeks of Ilaris treatment from studies G2305, G2301 and the extension study were pooled to assess maintenance of efficacy. These data showed similar improvements from baseline to week 12 in the adapted paediatric ACR responses and its components to those observed in the placebo controlled study (G2305). At week 12, the adapted paediatric ACR30, 50, 70, 90 and 100 responses were: 70%, 69%, 61%, 49% and 30%, respectively and 28% of patients had inactive disease (N=178).

The efficacy observed in the studies G2305 and G2301 was maintained in the ongoing, open-label long-term extension study (data available through median of 49 weeks of follow-up). In this study, 25 patients who had a strong ACR response for a minimum of 5 months reduced their Ilaris dose to 2 mg/kg every 4 weeks and maintained a paediatric ACR100 response throughout the time the reduced dose was given (median 32 weeks, 8-124 weeks).

Although limited, evidence from the clinical trials suggests that patients not responding to tocilizumab or anakinra, may respond to canakinumab.

SJIA in young adults and AOSD
Efficacy of Ilaris in a subset of young adult SJIA patients aged 16 to 20 years was consistent with the efficacy observed for patients less than 16 years of age. The efficacy profile in AOSD patients is expected to be similar to SJIA patients based on literature reports.

Gouty arthritis
The efficacy of Ilaris for the treatment of acute gouty arthritis attacks was demonstrated in two multicentre, randomised, double-blind, active-controlled studies in patients with frequent gouty arthritis (≥ 3 attacks in the previous 12 months) unable to use NSAIDs or colchicine (due to contraindication, intolerance or lack of efficacy). The studies were 12 weeks followed by 12-week double-blind extension. A total of 225 patients were treated with subcutaneous Ilaris 150 mg and 229 patients were treated with intramuscular triamcinolone acetonide (TA) 40 mg at study entry, and when experiencing a new attack thereafter. The mean number of gouty arthritis attacks in the previous 12 months was 6.5. Over 85% of patients had comorbidity, including hypertension (60%), diabetes (15%), ischaemic heart disease (12%), and stage ≥ 3 chronic kidney disease (25%). Approximately one-third of the patients enrolled (76 [33.8%] in the Ilaris group and 84 [36.7%] in the triamcinolone acetonide group) had documented inability (intolerance, contraindication or lack of response) to use both NSAIDs and colchicine. Concomitant treatment with ULTs was reported by 42% of patients at entry.

The co-primary endpoints were: (i) gouty arthritis pain intensity (visual analogue scale, VAS) at 72 hours post-dose, and (ii) time to first new gouty arthritis attack.

For the overall study population, pain intensity was statistically significantly lower for Ilaris 150 mg compared with triamcinolone acetonide at 72 hours. Ilaris also reduced the risk of subsequent attacks (see Table 4).

Efficacy results in a subgroup of patients unable to use both NSAIDs and colchicine and who were on ULT, failed ULT or had a contraindication to ULT (N=101) were consistent with the overall study population with a statistically significant difference compared to triamcinolone acetonide in pain intensity at 72 hours (-10.2 mm, p=0.0208) and in reduction of risk of subsequent attacks (Hazard ratio 0.39, p=0.0047 at 24 weeks).

Efficacy results for a more stringent subgroup limited to current users of ULT (N=62) are presented in Table 4. Treatment with Ilaris induced a reduction of pain and reduced the risk of subsequent attacks in patients using ULT and unable to use both NSAIDs and colchicine, although the observed treatment

difference compared to triamcinolone acetonide was less pronounced than with the overall study population.

Table 4 Efficacy for the overall study population and in a subgroup of patients currently using ULT and unable to use both NSAIDs and colchicine

Efficacy endpoint	Overall study population; N=454	Unable to use both NSAIDs and colchicine; on ULT N=62
Treatment of gouty arthritis attacks as measured by pain intensity (VAS) at 72 h		
Least Squares mean estimated difference to triamcinolone acetonide	-10.7	-3.8
CI	(-15.4, -6.0)	(-16.7, 9.1)
p-value, 1-sided	p < 0.0001*	p=0.2798
Risk reduction of subsequent gouty arthritis attacks as measured by time to first new flare (24 weeks)		
Hazard ratio to triamcinolone acetonide	0.44	0.71
CI	(0.32, 0.60)	(0.29, 1.77)
p-value, 1-sided	p < 0.0001*	p=0.2337
* Denotes significant p-value ≤ 0.025		

Safety results showed an increased incidence of adverse events for canakinumab compared to triamcinolone acetonide, with 66% vs 53% of patients reporting any adverse event and 20% vs 10% of patients reporting an infection adverse event over 24 weeks.

Elderly population
Overall, the efficacy, safety and tolerability profile of Ilaris in elderly patients ≥ 65 years of age was comparable to patients < 65 years of age.

Patients on urate lowering therapy (ULT)
In clinical studies, Ilaris has been safely administered with ULT. In the overall study population, patients on ULT had a less pronounced treatment difference in both pain reduction and reduction in the risk of subsequent gouty arthritis attacks compared to patients not on ULT.

Immunogenicity
Antibodies against Ilaris were observed in approximately 1.5%, 3% and 2% of the patients treated with Ilaris for CAPS, SJIA and gouty arthritis, respectively. No neutralising antibodies were detected. No apparent correlation of antibody development to clinical response or adverse events was observed.

This medicinal product has been authorised for CAPS under "Exceptional Circumstances". This means that due to the rarity of the disease it has not been possible to obtain complete information on this medicinal product. The European Medicines Agency will review any new information which may become available every year and this SmPC will be updated as necessary.

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with Ilaris in one or more subsets of the paediatric population in Cryopyrin Associated Periodic Syndromes (CAPS) and Juvenile Idiopathic Arthritis (see section 4.2 for information on paediatric use).

The European Medicines Agency has waived the obligation to submit the results of studies with Ilaris in all subsets of the paediatric population in gouty arthritis (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

CAPS

Absorption

The peak serum canakinumab concentration (C_{max}) occurred approximately 7 days following single subcutaneous administration of 150 mg in adult CAPS patients. The mean terminal half-life was 26 days. Mean values for C_{max} and AUC_{inf} after a single subcutaneous dose of 150 mg in a typical adult CAPS patient (70 kg) were 15.9 µg/ml and 708 µg*d/ml. The absolute bioavailability of subcutaneously administered canakinumab was estimated to be 66%. Exposure parameters (such as AUC and C_{max}) increased in proportion to dose over the dose range of 0.30 to 10.0 mg/kg given as intravenous infusion or from 150 to 600 mg as subcutaneous injection. Predicted steady-state exposure values ($C_{min,ss}$, $C_{max,ss}$, $AUC_{,ss,8w}$) after 150 mg subcutaneous administration (or 2 mg/kg, respectively) every 8 weeks were slightly higher in the weight category 40-70 kg (6.6 µg/ml, 24.3 µg/ml, 767 µg*d/ml) compared to the weight categories < 40 kg (4.0 µg/ml, 19.9 µg/ml, 566 µg*d/ml) and > 70 kg (4.6 µg/ml, 17.8 µg/ml, 545 µg*d/ml). The expected accumulation ratio was 1.3-fold following 6 months of subcutaneous administration of 150 mg canakinumab every 8 weeks.

Distribution

Canakinumab binds to serum IL-1 beta. The distribution volume (V_{ss}) of canakinumab varied according to body weight. It was estimated to be 6.2 litres in a CAPS patient of body weight 70 kg.

Elimination

The apparent clearance (CL/F) of canakinumab increases with body weight. It was estimated to be 0.17 l/d in a CAPS patient of body weight 70 kg and 0.11 l/d in a SJIA patient of body weight 33 kg. After accounting for body weight differences, no clinically significant differences in the pharmacokinetic properties of canakinumab were observed between CAPS and SJIA patients.

There was no indication of accelerated clearance or time-dependent change in the pharmacokinetic properties of canakinumab following repeated administration. No gender or age-related pharmacokinetic differences were observed after correction for body weight.

Still's Disease (AOSD and SJIA)

Bioavailability in SJIA patients has not been determined independently. Apparent clearance per kg body weight (CL/F per kg) was comparable between the SJIA and CAPS population (0.004 l/d per kg). The apparent volume of distribution per kg (V/F per kg) was 0.14 l/kg.

After repeated administration of 4 mg/kg every 4 weeks the accumulation ratio of canakinumab was 1.6 fold in SJIA patients. Steady state was reached after 110 days. The overall predicted mean (±SD) for $C_{min,ss}$, $C_{max,ss}$ and $AUC_{,ss4w}$ were 14.7±8.8 µg/ml, 36.5 ± 14.9 µg/ml and 696.1 ± 326.5 µg*d/ml, respectively.

The AUC_{ss4w} in each age group was 692, 615, 707 and 742 µg*d/ml for 2-3, 4-5, 6-11, and 12-19 years old, respectively. When stratified by weight, a lower (30-40%) median of exposure for $C_{min,ss}$ (11.4 vs 19 µg/ml) and AUC_{ss} (594 vs 880 µg*d/ml) for the lower bodyweight category (≤ 40 kg) vs the higher bodyweight category (> 40 kg) was observed.

Based on the population pharmacokinetic modelling analysis, the pharmacokinetics of canakinumab in young adult SJIA patients aged 16 to 20 years were similar to those in patients less than 16 years of age. Predicted canakinumab steady state exposures at a dose level of 4 mg/kg (maximum 300 mg) in patients over the age of 20 years were comparable to those in SJIA patients younger than 20 years of age.

Gouty arthritis population

Bioavailability in gouty arthritis patients has not been determined independently. Apparent clearance per kg body weight (CL/F per kg) was comparable between the gouty arthritis and CAPS population (0.004 l/d/kg). Mean exposure in a typical gouty arthritis patient (93 kg) after a single subcutaneous 150 mg dose (C_{max}: 10.8 µg/ml and AUC_{inf}: 495 µg*d/ml) was lower than in a typical 70 kg CAPS

patient (15.9 µg/ml and 708 µg*d/ml). This is consistent with the observed increase in CL/F with body weight.

The expected accumulation ratio was 1.1-fold following subcutaneous administration of 150 mg canakinumab every 12 weeks.

Paediatric population
Peak concentrations of canakinumab occurred between 2 to 7 days (T_{max}) following single subcutaneous administration of canakinumab 150 mg or 2 mg/kg in paediatric patients 4 years of age and older. The terminal half-life ranged from 22.9 to 25.7 days, similar to the pharmacokinetic properties observed in adults. Based on the population pharmacokinetic modelling analysis, the pharmacokinetics of canakinumab in children aged 2 to < 4 years were similar to those in patients 4 years of age and older. Subcutaneous absorption rate was estimated to decrease with age and appeared to be fastest in the youngest patients. Accordingly, T_{max} was shorter (3.6 days) in younger SJIA patients (2-3 years) compared to older SJIA patients (12-19 years; T_{max} 6 days). Bioavailability (AUC_{ss}) was not affected.

An additional pharmacokinetics analysis showed that the pharmacokinetics of canakinumab in 6 paediatric CAPS patients under the age of 2 years were similar to the pharmacokinetics in paediatric patients 2-4 years of age. Based on the population pharmacokinetic modelling analysis, the expected exposures after a dose of 2 mg/kg were comparable across the CAPS paediatric age groups, but were approximately 40% lower in paediatric patients of very low body weight (e.g., 10 kg) than in adult patients (150 mg dose). This is consistent with the observations of higher exposure in higher body weight groups in CAPS patients.

Pharmacokinetic properties are similar in CAPS and SJIA paediatric populations.

Elderly population
No change in pharmacokinetic parameters based on clearance or volume of distribution were observed between elderly patients and adult patients < 65 years of age.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on cross-reactivity, repeated dose, immunotoxicity, reproductive and juvenile toxicity studies performed with canakinumab or a murine anti-murine IL-1 beta antibody.

Since canakinumab binds to marmoset (*C. jacchus*) and human IL-1 beta with a similar affinity, the safety of canakinumab has been studied in the marmoset. No undesirable effects of canakinumab were seen following twice weekly administration to marmosets for up to 26 weeks or in an embryofoetal developmental toxicity study in pregnant marmosets. Plasma concentrations that are well tolerated in animals are in excess of at least 42-fold (C_{max}) and 78-fold (C_{avg}) the plasma concentrations in paediatric CAPS patients (body weight 10 kg) treated with clinical doses of canakinumab up to 8 mg/kg subcutaneously every 8 weeks. Plasma concentrations that are well tolerated in animals exceed at least 62-fold (C_{max}) and 104-fold (C_{avg}) the plasma concentrations in paediatric SJIA patients, treated with up to 4 mg/kg via the subcutaneous route every 4 weeks. In addition, no antibodies to canakinumab were detected in these studies. No non-specific tissue cross-reactivity was demonstrated when canakinumab was applied to normal human tissues.

Formal carcinogenicity studies have not been conducted with canakinumab.

In an embryofoetal development study in marmosets canakinumab showed no maternal toxicity, embryotoxicity or teratogenicity when administered throughout organogenesis.

No undesirable effects of a murine anti-murine IL-1 beta antibody were seen in a complete set of reproductive and juvenile studies in mice. Anti-murine IL-1 beta did not elicit adverse events on foetal or neonatal growth when administered throughout late gestation, delivery and nursing (see section 4.6).

The high dose used in these studies was in excess of the maximally effective dose in terms of IL-1 beta suppression and activity.

An immunotoxicology study in mice with a murine anti-murine IL-1 beta antibody showed that neutralising IL-1 beta has no effects on immune parameters and caused no impairment of immune function in mice.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Histidine
Histidine hydrochloride monohydrate
Polysorbate 80

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years.

After reconstitution, from a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).
Do not freeze.
Store in the original package in order to protect from light.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

150 mg of powder for solution for injection in a vial (type I glass) with a stopper (coated chlorobutyl rubber) and flip-off cap (aluminium).

Packs containing 1 vial or multipacks containing 4 (4x1) vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Ilaris 150 mg powder for solution for injection is supplied in a single-use vial for individual use. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Instructions for reconstitution
Using aseptic technique, reconstitute each vial of Ilaris at room temperature (typically 15°C to 25°C) by slowly injecting 1.0 ml water for injections with a 1 ml syringe and an
18 G x 2 inch (50 mm) needle. Swirl the vial slowly at an angle of about 45° for approximately

1 minute and allow to stand for about 5 minutes. Then gently turn the vial upside down and back again ten times. If possible, avoid touching the rubber stopper with your fingers. Allow to stand for about 15 minutes at room temperature to obtain a clear to opalescent solution. Do not shake. Do not use if particles are present in the solution.

Tap the side of the vial to remove any residual liquid from the stopper. The solution should be free of visible particles and clear to opalescent. The solution should be colourless or may have a slight brownish-yellow tint. If the solution has a distinctly brown discolouration it should not be used. If not used immediately after reconstitution, the solution should be kept at 2°C to 8°C and used within 24 hours.

Instructions for administration
Carefully withdraw the required volume depending on the dose to be administered (0.2 ml to 1.0 ml) and subcutaneously inject using a 27 G x 0.5 inch (13 mm) needle.

The following are suitable injection sites: upper thigh, abdomen, upper arm or buttocks. Broken skin and areas which are bruised or covered by a rash should be avoided. Injection into scar-tissue should be avoided as this may result in insufficient exposure to Ilaris.

Disposal
Patients or their caregivers should be instructed on the appropriate procedure for disposal of the vials, syringes and needles in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/564/001-002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 October 2009
Date of latest renewal: 19 June 2014

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Ilaris 150 mg powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains 150 mg of canakinumab*.

After reconstitution, each ml of solution contains 150 mg canakinumab.

* fully human monoclonal antibody produced in mouse hybridoma Sp2/0 cells by recombinant DNA technology

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.
The powder is white.
The solvent is clear and colourless.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Cryopyrin-Associated Periodic Syndromes
Ilaris is indicated for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS) in adults, adolescents and children aged 2 years and older with body weight of 7.5 kg or above, including:
- Muckle-Wells Syndrome (MWS),
- Neonatal-Onset Multisystem Inflammatory Disease (NOMID) / Chronic Infantile Neurological, Cutaneous, Articular Syndrome (CINCA),
- Severe forms of Familial Cold Autoinflammatory Syndrome (FCAS) / Familial Cold Urticaria (FCU) presenting with signs and symptoms beyond cold-induced urticarial skin rash.

Still's Disease
Ilaris is indicated for the treatment of active Still's disease including Adult-Onset Still's Disease (AOSD) and Systemic Juvenile Idiopathic Arthritis (SJIA) in patients aged 2 years and older who have responded inadequately to previous therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids. Ilaris can be given as monotherapy or in combination with methotrexate.

Gouty arthritis
Ilaris is indicated for the symptomatic treatment of adult patients with frequent gouty arthritis attacks (at least 3 attacks in the previous 12 months) in whom non-steroidal anti-inflammatory drugs (NSAIDs) and colchicine are contraindicated, are not tolerated, or do not provide an adequate response, and in whom repeated courses of corticosteroids are not appropriate (see section 5.1).

4.2 Posology and method of administration

For CAPS and Still's disease, the treatment should be initiated and supervised by a specialist physician experienced in the diagnosis and treatment of the relevant indication.

For gouty arthritis, the physician should be experienced in the use of biologics and Ilaris should be administered by a healthcare professional.

After proper training in the correct injection technique, patients or their caregivers may inject Ilaris if the physician determines that it is appropriate and with medical follow-up as necessary (see section 6.6).

Posology
CAPS: Adults, adolescents and children aged 2 years and older
The recommended starting dose of Ilaris for CAPS patients is:
Adults, adolescents and children ≥ 4 years of age:
- 150 mg for patients with body weight > 40 kg
- 2 mg/kg for patients with body weight ≥ 15 kg and ≤ 40 kg
- 4 mg/kg for patients with body weight ≥ 7.5 kg and < 15 kg

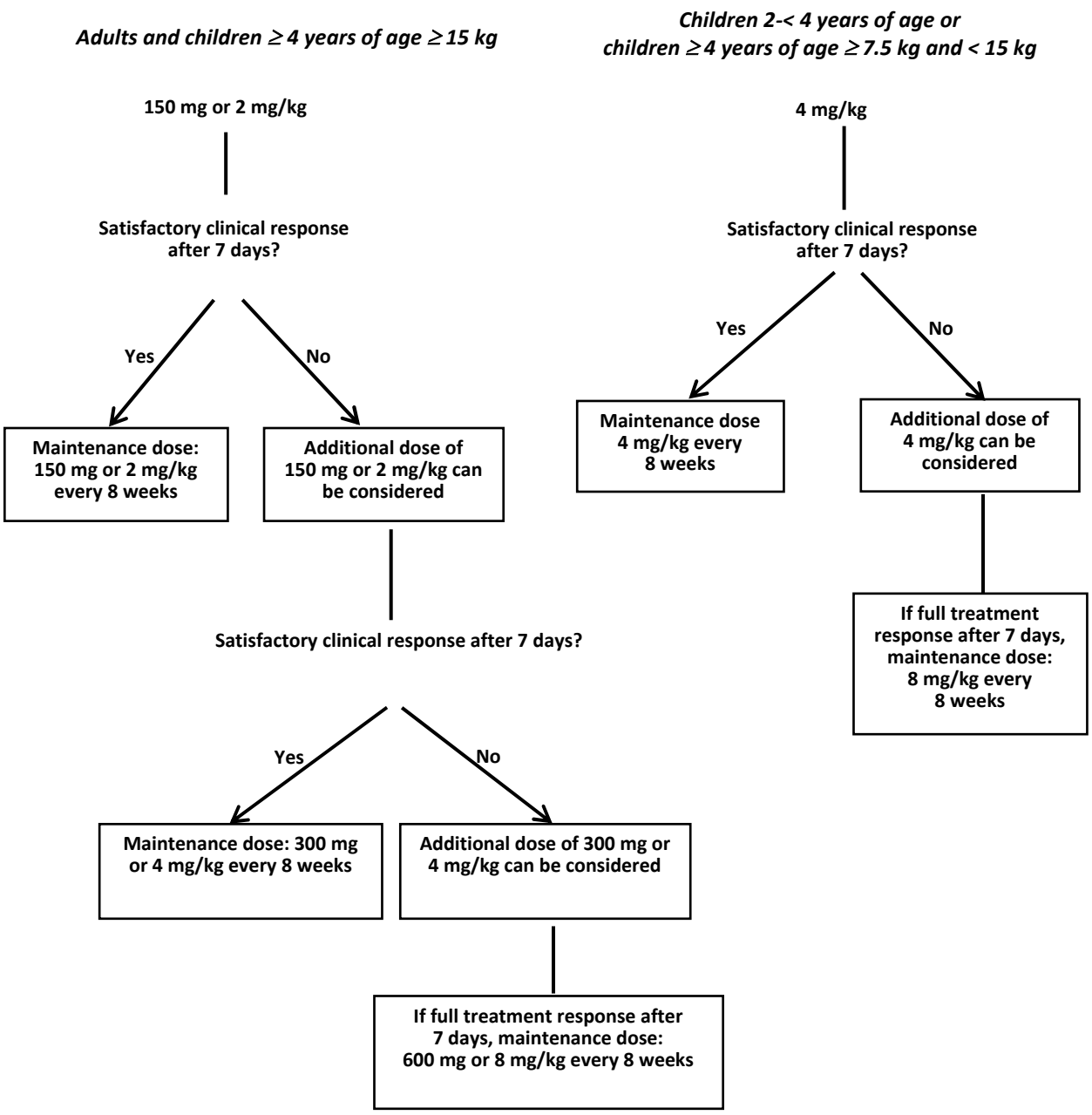
Children 2 to < 4 years of age:
- 4 mg/kg for patients with body weight ≥ 7.5 kg

This is administered every eight weeks as a single dose via subcutaneous injection.

For patients with a starting dose of 150 mg or 2 mg/kg, if a satisfactory clinical response (resolution of rash and other generalised inflammatory symptoms) has not been achieved 7 days after treatment start, a second dose of Ilaris at 150 mg or 2 mg/kg can be considered. If a full treatment response is subsequently achieved, the intensified dosing regimen of 300 mg or 4 mg/kg every 8 weeks should be maintained. If a satisfactory clinical response has not been achieved 7 days after this increased dose, a third dose of Ilaris at 300 mg or 4 mg/kg can be considered. If a full treatment response is subsequently achieved, maintaining the intensified dosing regimen of 600 mg or 8 mg/kg every 8 weeks should be considered, based on individual clinical judgement.

For patients with a starting dose of 4 mg/kg, if a satisfactory clinical response has not been achieved 7 days after treatment start, a second dose of Ilaris 4 mg/kg can be considered. If a full treatment response is subsequently achieved, maintaining the intensified dosing regimen of 8 mg/kg every 8 weeks should be considered, based on individual clinical judgement.

Clinical experience with dosing at intervals of less than 4 weeks or at doses above 600 mg or 8 mg/kg is limited.



Still's Disease (AOSD and SJIA)
The recommended dose of Ilaris for patients with Still's disease (AOSD and SJIA) with body weight ≥ 7.5 kg is 4 mg/kg (up to a maximum of 300 mg) administered every four weeks via subcutaneous injection. Continued treatment with Ilaris in patients without clinical improvement should be reconsidered by the treating physician.

Gouty arthritis
Management of hyperuricaemia with appropriate urate lowering therapy (ULT) should be instituted or optimised. Ilaris should be used as an on-demand therapy to treat gouty arthritis attacks.

The recommended dose of Ilaris for adult patients with gouty arthritis is 150 mg administered subcutaneously as a single dose during an attack. For maximum effect, Ilaris should be administered as soon as possible after the onset of a gouty arthritis attack.

Patients who do not respond to initial treatment should not be re-treated with Ilaris. In patients who respond and require re-treatment, there should be an interval of at least 12 weeks before a new dose of Ilaris may be administered (see section 5.2).

Special populations
Paediatric population
CAPS
The safety and efficacy of Ilaris in CAPS patients under 2 years of age have not been established. Currently available data are described in sections 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

SJIA
The safety and efficacy of Ilaris in SJIA patients under 2 years of age have not been established.

Gouty arthritis
There is no relevant use of Ilaris in the paediatric population in the indication gouty arthritis.

Elderly
No dose adjustment is required.

Hepatic impairment
Ilaris has not been studied in patients with hepatic impairment.

Renal impairment
No dose adjustment is needed in patients with renal impairment. However, clinical experience in such patients is limited.

Method of Administration
Ilaris is to be administered via subcutaneous injection. For instructions on use and handling of the reconstituted solution, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Active, severe infections (see section 4.4).

4.4 Special warnings and precautions for use

Infections
Ilaris is associated with an increased incidence of serious infections. Therefore patients should be monitored carefully for signs and symptoms of infections during and after treatment with Ilaris. Physicians should exercise caution when administering Ilaris to patients with infections, a history of recurring infections, or underlying conditions which may predispose them to infections.

Treatment of CAPS and Still's Disease (AOSD and SJIA)
Ilaris should not be initiated or continued in patients during an active infection requiring medical intervention.

Treatment of gouty arthritis
Ilaris should not be administered during an active infection.

Concomitant use of Ilaris with tumour necrosis factor (TNF) inhibitors is not recommended because this may increase the risk of serious infections (see section 4.5).

Isolated cases of unusual or opportunistic infections (including aspergillosis, atypical mycobacterial infections, herpes zoster) have been reported during Ilaris treatment. The causal relationship of Ilaris to these events cannot be excluded.

In approximately 12% of CAPS patients tested with a PPD (purified protein derivative) skin test in clinical trials, follow-up testing yielded a positive test result while treated with Ilaris without clinical evidence of a latent or active tuberculosis infection.

It is unknown whether the use of interleukin-1 (IL-1) inhibitors such as Ilaris increases the risk of reactivation of tuberculosis. Before initiation of therapy, all patients must be evaluated for both active and latent tuberculosis infection. Particularly in adult patients, this evaluation should include a detailed medical history. Appropriate screening tests (e.g. tuberculin skin test, interferon gamma release assay or chest X-ray) should be performed in all patients (local recommendations may apply). Patients must be monitored closely for signs and symptoms of tuberculosis during and after treatment with Ilaris. All patients should be instructed to seek medical advice if signs or symptoms suggestive of tuberculosis (e.g. persistent cough, weight loss, subfebrile temperature) appear during Ilaris therapy. In the event of conversion from a negative to a positive PPD test, especially in high-risk patients, alternative means of screening for a tuberculosis infection should be considered.

Neutropenia and leukopenia
Neutropenia (absolute neutrophil count [ANC] < 1.5 x 10^9/l) and leukopenia have been observed with medicinal products that inhibit IL-1, including Ilaris. Treatment with Ilaris should not be initiated in patients with neutropenia or leukopenia. It is recommended that white blood cell (WBC) counts including neutrophil counts be assessed prior to initiating treatment and again after 1 to 2 months. For chronic or repeated therapies, it is also recommended to assess WBC counts periodically during treatment. If a patient becomes neutropenic or leukopenic, the WBC counts should be monitored closely and treatment discontinuation should be considered.

Malignancies
Malignancy events have been reported in patients treated with Ilaris. The risk for the development of malignancies with anti-interleukin (IL)-1 therapy is unknown.

Hypersensitivity reactions
Hypersensitivity reactions with Ilaris therapy have been reported. The majority of these events were mild in severity. During clinical development of Ilaris in over 2,300 patients, no anaphylactoid or anaphylactic reactions were reported. However, the risk of severe hypersensitivity reactions, which is not uncommon for injectable proteins, cannot be excluded (see section 4.3).

Hepatic function
Transient and asymptomatic cases of elevations of serum transaminases or bilirubin have been reported in clinical trials (see section 4.8).

Vaccinations
No data are available on the risk of secondary transmission of infection by live (attenuated) vaccines in patients receiving Ilaris. Therefore, live vaccines should not be given concurrently with Ilaris unless the benefits clearly outweigh the risks (see section 4.5).

Prior to initiation of Ilaris therapy it is recommended that adult and paediatric patients receive all vaccinations, as appropriate, including pneumococcal vaccine and inactivated influenza vaccine (see section 4.5).

Mutation in NLRP3 gene in CAPS patients
Clinical experience in CAPS patients without a confirmed mutation in the NLRP3 gene is limited.

Macrophage activation syndrome in patients with Still's Disease
Macrophage activation syndrome (MAS) is a known, life-threatening disorder that may develop in patients with rheumatic conditions, in particular Still's disease. If MAS occurs, or is suspected, evaluation and treatment should be started as early as possible. Physicians should be attentive to symptoms of infection or worsening of Still's disease, as these are known triggers for MAS. Based on clinical trial experience, Ilaris does not appear to increase the incidence of MAS in SJIA patients, but no definitive conclusion can be made.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions between Ilaris and other medicinal products have not been investigated in formal studies.

An increased incidence of serious infections has been associated with administration of another IL-1 blocker in combination with TNF inhibitors. Use of Ilaris with TNF inhibitors is not recommended because this may increase the risk of serious infections.

The expression of hepatic CYP450 enzymes may be suppressed by the cytokines that stimulate chronic inflammation, such as interleukin-1 beta (IL-1 beta). Thus, CYP450 expression may be reversed when potent cytokine inhibitory therapy, such as canakinumab, is introduced. This is clinically relevant for CYP450 substrates with a narrow therapeutic index where the dose is individually adjusted. On initiation of canakinumab in patients being treated with this type of medicinal product, therapeutic monitoring of the effect or of the active substance concentration should be performed and the individual dose of the medicinal product adjusted as necessary.

No data are available on either the effects of live vaccination or the secondary transmission of infection by live vaccines in patients receiving Ilaris. Therefore, live vaccines should not be given concurrently with Ilaris unless the benefits clearly outweigh the risks. Should vaccination with live vaccines be indicated after initiation of Ilaris treatment, the recommendation is to wait for at least 3 months after the last Ilaris injection and before the next one (see section 4.4).

The results of a study in healthy adult subjects demonstrated that a single dose of Ilaris 300 mg did not affect the induction and persistence of antibody responses after vaccination with influenza or glycosylated protein based meningococcus vaccines.

The results of a 56-week, open label study in CAPS patients aged 4 years and younger demonstrated that all patients who received non-live, standard of care childhood vaccinations developed protective antibody levels.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females
Women should use effective contraceptives during treatment with Ilaris and for up to 3 months after the last dose.

Pregnancy
There is a limited amount of data from the use of canakinumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). The risk for the foetus/mother is unknown. Women who are pregnant or who desire to become pregnant should therefore only be treated after a thorough benefit-risk evaluation.

Animal studies indicate that canakinumab crosses the placenta and is detectable in the foetus. No human data are available, but as canakinumab is an immunoglobulin of the G class (IgG1), human transplacental transfer is expected. The clinical impact of this is unknown. However, administration of live vaccines to newborn infants exposed to canakinumab *in utero* is not recommended for 16 weeks following the mother's last dose of Ilaris before childbirth. Women who received canakinumab during pregnancy should be instructed to inform the baby's healthcare professional before any vaccinations are given to their newborn infant.

Breast-feeding
It is unknown whether canakinumab is excreted in human milk. The decision whether to breast-feed during Ilaris therapy should therefore only be taken after a thorough benefit-risk evaluation.

Animal studies have shown that a murine anti-murine IL-1 beta antibody had no undesirable effects on development in nursing mouse pups and that the antibody was transferred to them (see section 5.3).

Fertility
Formal studies of the potential effect of Ilaris on human fertility have not been conducted. Canakinumab had no effect on male fertility parameters in marmosets (*C. jacchus*). A murine anti-murine IL-1 beta antibody had no undesirable effects on fertility in male or female mice (see section 5.3).

4.7 Effects on ability to drive and use machines

Ilaris has minor influence on the ability to drive and use machines. Treatment with Ilaris may result in dizziness/vertigo or asthenia (see section 4.8). Patients who experience such symptoms during Ilaris treatment should wait for this to resolve completely before driving or operating machines.

4.8 Undesirable effects

Summary of the safety profile
Over 2,400 subjects including approximately 380 children (aged 2 to 17 years) have been treated with Ilaris in interventional studies in patients with CAPS, SJIA, gouty arthritis or other IL-1 beta mediated diseases, and healthy volunteers. Serious infections have been observed. The most frequent adverse drug reactions were infections predominantly of the upper respiratory tract. The majority of the events were mild to moderate. No impact on the type or frequency of adverse drug reactions was seen with longer-term treatment.

Hypersensitivity reactions have been reported in patients treated with Ilaris (see sections 4.3 and 4.4).

Opportunistic infections have been reported in patients treated with Ilaris (see section 4.4).

CAPS
A total of 211 adult and paediatric CAPS patients (including FCAS/FCU, MWS, and NOMID/CINCA) have received Ilaris in clinical trials. The safety of Ilaris compared with placebo was investigated in a pivotal phase III trial that consisted of an 8-week, open-label period (Part I), a 24-week, randomised, double-blind and placebo-controlled withdrawal period (Part II), and a 16-week open label period on Ilaris (Part III). All patients were treated with Ilaris 150 mg subcutaneous or 2 mg/kg if body weight was ≥ 15 kg and ≤ 40 kg.

Still's Disease
A total of 324 SJIA patients aged 2 to < 20 years have received Ilaris in clinical trials, including 293 patients aged 2 to < 16 years old, 21 patients aged 16 to < 18 years old and 10 patients aged 18 to < 20 years old. The safety of Ilaris compared to placebo was investigated in two pivotal Phase III studies (see section 5.1).

Gouty arthritis
More than 700 patients with gouty arthritis have been treated with Ilaris at doses from 10 mg to 300 mg in randomised, double-blind and active-controlled clinical trials of up to 24 weeks' duration. More than 250 patients have been treated with the recommended dose of 150 mg in Phase II and III trials (see section 5.1).

Tabulated list of adverse reactions
Adverse reactions are listed according to MedDRA system organ class. Within each system organ class, the adverse reactions are ranked by frequency category with the most common first. Frequency categories are defined using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1 Tabulated list of adverse reactions in CAPS, SJIA and gouty arthritis

MedDRA System Organ Class	CAPS	SJIA	Gouty arthritis
Infections and infestations			
Very Common	Nasopharyngitis	Pneumonia Gastroenteritis Urinary tract infection Viral infection Sinusitis Rhinitis Pharyngitis Tonsilitis Nasopharyngitis Upper respiratory tract infection	Pneumonia Bronchitis Gastroenteritis Urinary tract infection Influenza Cellulitis Sinusitis Ear infection Pharyngitis Nasopharyngitis Upper respiratory tract infection
Common	Urinary tract infection Upper respiratory tract infection Viral infection		
Nervous system disorders			
Common	Dizziness/vertigo		Dizziness/vertigo
Gastrointestinal disorders			
Very common		Abdominal pain (upper)	
Uncommon			Gastro-oesophageal reflux disease
Skin and subcutaneous tissue disorders			
Very common	Injection site reaction	Injection site reaction	
Common			Injection site reaction
Musculoskeletal and connective tissue disorders			
Very common		Arthralgia	
Common		Musculoskeletal pain	Back pain
General disorders and administration site conditions			
Common			Fatigue/asthenia
Investigations			
Very common		Creatinine renal clearance decreased * Proteinuria # Leukopenia	
Common		Neutropenia	
* based on estimated creatinine clearance, most were transient # most represented transient trace to 1+ positive urinary protein by dipstick			

In a subset of young adult SJIA patients aged 16 to 20 years (n=31), the safety profile of Ilaris was consistent with what was observed in SJIA patients less than 16 years of age. The safety profile in AOSD patients is expected to be similar to SJIA patients based on literature reports.

Description of selected adverse reactions

Long-term data and laboratory abnormalities in CAPS patients

During clinical trials with Ilaris in CAPS patients mean values for haemoglobin increased and those for white blood cell, neutrophils and platelets decreased.

Elevations of transaminases have been observed rarely in CAPS patients.

Asymptomatic and mild elevations of serum bilirubin have been observed in CAPS patients treated with Ilaris without concomitant elevations of transaminases.

In the long-term, open-label studies with dose escalation, events of infections (gastroenteritis, respiratory tract infection, upper respiratory tract infection), vomiting and dizziness were more frequently reported in the 600 mg or 8 mg/kg dose group than in other dose groups.

Laboratory abnormalities in SJIA patients
Haematology
In the overall SJIA program, transient decreased white blood cell (WBC) counts ≤ 0.8 x LLN were reported in 33 patients (16.5%).

In the overall SJIA program, transient decreases in absolute neutrophil count (ANC) to less than 1 x 10^9/l were reported in 12 patients (6.0%).

In the overall SJIA program, transient decreases in platelet counts (< LLN) were observed in 19 patients (9.5%).

ALT/AST
In the overall SJIA program, high ALT and/or AST > 3 x upper limit of normal (ULN) were reported in 19 patients (9.5%).

Laboratory abnormalities in gouty arthritis patients
Haematology
Decreased white blood cell counts (WBC) ≤ 0.8 x lower limit of normal (LLN) were reported in 6.7% of patients treated with Ilaris compared to 1.4% treated with triamcinolone acetonide. Decreases in absolute neutrophil counts (ANC) to less than 1 x 10^9/l were reported in 2% of patients in the comparative trials. Isolated cases of ANC counts < 0.5 x 10^9/l were also observed (see section 4.4).

Mild (< LLN and > 75 x 10^9/l) and transient decreases in platelet counts were observed at a higher incidence (12.7%) with Ilaris in the active-controlled clinical studies versus the comparator (7.7%) in gouty arthritis patients.

Uric acid
Increases in uric acid level (0.7 mg/dl at 12 weeks and 0.5 mg/dl at 24 weeks) were observed after Ilaris treatment in comparative trials in gouty arthritis. In another study, among patients who were starting on ULT, increases in uric acid were not observed. Uric acid increases were not observed in clinical trials in non-gouty arthritis populations (see section 5.1).

ALT/AST
Mean and median increases in alanine transaminase (ALT) of 3.0 U/l and 2.0 U/l, respectively, and in aspartate transaminase (AST) of 2.7 U/l and 2.0 U/l, respectively, from baseline to end of study were seen in the Ilaris-treated groups versus the triamcinolone acetonide-treated group(s), however the incidence of clinically significant changes (≥ 3 x the upper limit of normal) was greater for patients treated with triamcinolone acetonide (2.5% for both AST and ALT) compared with Ilaris-treated patients (1.6% for ALT and 0.8% for AST).

Triglycerides
In active-controlled gouty arthritis trials, there was a mean increase in triglycerides of 33.5 mg/dl in Ilaris-treated patients compared with a modest decrease of -3.1 mg/dl with triamcinolone acetonide. The incidence of patients with triglyceride elevations > 5 x upper limit of normal (ULN) was 2.4% with Ilaris and 0.7% with triamcinolone acetonide. The clinical significance of this observation is unknown.

Paediatric population
There were 80 paediatric CAPS patients (2-17 years of age) included in the studies. Overall, there were no clinically meaningful differences in the safety and tolerability profile of Ilaris in paediatric patients compared to the overall CAPS population (comprised of adult and paediatric patients, N=211), including the overall frequency and severity of infectious episodes. Infections of the upper respiratory tract were the most frequently reported infection events.

Additionally, 6 paediatric patients under the age of 2 years were evaluated in a small open-label clinical study. The safety profile of Ilaris appeared similar to that in patients aged 2 years and above.

Elderly population
There is no significant difference in safety profile observed in patients ≥ 65 years of age.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Reported experience with overdose is limited. In early clinical trials, patients and healthy volunteers received doses as high as 10 mg/kg, administered intravenously or subcutaneously, without evidence of acute toxicity.

In case of overdose, it is recommended for the patient to be monitored for any signs or symptoms of adverse reactions, and appropriate symptomatic treatment instituted immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, interleukin inhibitors, ATC code: L04AC08

Mechanism of action
Canakinumab is a fully human monoclonal anti-human interleukin-1 beta (IL-1 beta) antibody of the IgG1/κ isotype. Canakinumab binds with high affinity specifically to human IL-1 beta and neutralises the biological activity of human IL-1 beta by blocking its interaction with IL-1 receptors, thereby preventing IL-1 beta-induced gene activation and the production of inflammatory mediators.

Pharmacodynamic effects
CAPS
In clinical studies, CAPS patients who have uncontrolled over-production of IL-1 beta show a rapid response to therapy with canakinumab, i.e. laboratory parameters such as high C-reactive protein (CRP) and serum amyloid A (SAA), high neutrophil and platelet counts, and leukocytosis rapidly returned to normal.

Still's Disease (AOSD and SJIA)
Adult-Onset Still's Disease and Systemic Juvenile Idiopathic Arthritis are severe autoinflammatory diseases, driven by innate immunity by means of pro-inflammatory cytokines, a key one being IL-1-beta.

Common features of AOSD and SJIA include fever, rash, hepatosplenomegaly, lymphadenopathy, polyserositis and arthritis. Treatment with canakinumab resulted in a rapid and sustained improvement of both the articular and the systemic features of SJIA with significant reduction of the number of

inflamed joints, prompt resolution of fever and reduction of acute phase reactants in the majority of patients (see Clinical efficacy and safety).

Gouty arthritis
A gouty arthritis attack is caused by urate (monosodium urate monohydrate) crystals in the joint and surrounding tissue, which trigger resident macrophages to produce IL-1 beta via the "NALP3 inflammasome" complex. Activation of macrophages and concomitant over-production of IL-1 beta results in an acute painful inflammatory response. Other activators of the innate immune system, such as endogenous agonists of toll-like receptors, may contribute to the transcriptional activation of the IL-1 beta gene, initiating a gouty arthritis attack. Following canakinumab treatment, the inflammatory markers CRP or SAA and signs of acute inflammation (e.g. pain, swelling, redness) in the affected joint subside rapidly.

Clinical efficacy and safety
CAPS
The efficacy and safety of Ilaris have been demonstrated in patients with varying degrees of disease severity and different CAPS phenotypes (including FCAS/FCU, MWS, and NOMID/CINCA). Only patients with confirmed NLRP3 mutation were included in the pivotal study.

In the Phase I/II study, treatment with Ilaris had a rapid onset of action, with disappearance or clinically significant improvement of symptoms within one day after dosing. Laboratory parameters such as high CRP and SAA, high neutrophils and platelet counts normalised rapidly within days of Ilaris injection.

The pivotal study consisted of a 48-week three-part multicentre study, i.e. an 8-week open-label period (Part I), a 24-week randomised, double-blind, placebo-controlled withdrawal period (Part II), followed by a 16-week open-label period (Part III). The aim of the study was to assess efficacy, safety, and tolerability of Ilaris (150 mg or 2 mg/kg every 8 weeks) in patients with CAPS.

- Part I: A complete clinical and biomarker response to Ilaris (defined as composite of physician's global assessment on autoinflammatory and on skin disease ≤ minimal and CRP or SAA values < 10 mg/litre) was observed in 97% of patients and appeared within 7 days of initiation of treatment. Significant improvements were seen in physician's clinical assessment of autoinflammatory disease activity: global assessment of autoinflammatory disease activity, assessment of skin disease (urticarial skin rash), arthralgia, myalgia, headache/migraine, conjunctivitis, fatigue/malaise, assessment of other related symptoms, and patient's assessment of symptoms.

- Part II: In the withdrawal period of the pivotal study, the primary endpoint was defined as the proportion of patients with a disease relapse/flare: none (0%) of the patients randomised to Ilaris flared, compared with 81% of the patients randomised to placebo.

- Part III: Patients treated with placebo in Part II who flared regained and maintained clinical and serological response following entry into the open-label Ilaris extension.

Table 2 Tabulated summary of efficacy in Phase III trial, pivotal placebo-controlled withdrawal period (Part II)

Phase III trial, pivotal placebo-controlled withdrawal period (Part II)			
	Ilaris N=15 n(%)	Placebo N=16 n(%)	p-value
Primary endpoint (flare)			
Proportion of patients with disease flare in Part II	0 (0%)	13 (81%)	< 0.001
Inflammatory markers*			
C-reactive protein, mg/l	1.10 (0.40)	19.93 (10.50)	< 0.001
Serum amyloid A, mg/l	2.27 (-0.20)	71.09 (14.35)	0.002
* mean (median) change from beginning of Part II			

Two open-label, uncontrolled, long-term phase III studies were performed. One was a safety, tolerability, and efficacy study of canakinumab in patients with CAPS. The total treatment duration ranged from 6 months to 2 years. The other was an open-label study with canakinumab to evaluate the efficacy and safety in Japanese CAPS patients for 24 weeks, with an extension phase up to 48 weeks. The primary objective was to assess the proportion of patients who were free of relapse at week 24, including those patients whose dose was increased.

In the pooled efficacy analysis for these two studies, 65.6% of patients who had not previously been treated with canakinumab achieved complete response at 150 mg or 2 mg/kg, while 85.2% of patients achieved complete response at any dose. Of the patients treated with 600 mg or 8 mg/kg (or even higher), 43.8% achieved complete response. Fewer patients aged 2 to < 4 years achieved complete response (57.1%) than older paediatric and adult patients. Of the patients who had achieved a complete response, 89.3% maintained response without relapsing.

Experience from individual patients who achieved a complete response following dose escalation to 600 mg (8 mg/kg) every 8 weeks suggests that a higher dose may be beneficial in patients not achieving complete response or not maintaining complete response with the recommended doses (150 mg or 2 mg/kg for patients ≥ 15 kg and ≤ 40 kg). An increased dose was administered more frequently to patients aged 2 to < 4 years and to patients with NOMID/CINCA symptoms compared with FCAS or MWS.

Paediatric population
The CAPS trials with Ilaris included a total of 80 paediatric patients with an age range from 2 to 17 years (approximately half of them treated on an mg/kg basis). Overall, there were no clinically meaningful differences in the efficacy, safety and tolerability profile of Ilaris in paediatric patients compared to the overall CAPS population. The majority of paediatric patients achieved improvement in clinical symptoms and objective markers of inflammation (e.g. SAA and CRP).

A 56-week, open-label study was conducted to assess the efficacy, safety and tolerability of Ilaris in paediatric CAPS patients ≤4 years of age. Seventeen patients (including 6 patients under the age of 2 years) were evaluated, using weight-based starting doses of 2-8 mg/kg. The study also evaluated the effect of canakinumab on the development of antibodies to standard childhood vaccines. No differences in safety or efficacy were observed in patients under the age of 2 years compared with patients aged 2 years and above. All patients who received non-live, standard of care childhood vaccinations (N=7) developed protective antibody levels.

Still's Disease
SJIA
The efficacy of Ilaris for the treatment of active SJIA was assessed in two pivotal studies (G2305 and G2301). Patients enrolled were aged 2 to < 20 years (mean age of 8.5 years and mean disease duration

of 3.5 years at baseline) and had active disease defined as ≥ 2 joints with active arthritis, fever and elevated CRP.

Study G2305
Study G2305 was a randomised, double-blind, placebo-controlled, 4-week study assessing the short-term efficacy of Ilaris in 84 patients randomised to receive a single dose of 4 mg/kg (up to 300 mg) Ilaris or placebo. The primary objective was the proportion of patients at day 15 who achieved a minimum 30% improvement in the paediatric American College of Rheumatology (ACR) response criterion adapted to include absence of fever. Ilaris treatment improved all paediatric ACR response scores as compared to placebo at days 15 and 29 (Table 3).

Table 3 Paediatric ACR response and disease status at days 15 and 29

	Day 15		Day 29	
	Ilaris N=43	Placebo N=41	Ilaris N=43	Placebo N=41
ACR30	84%	10%	81%	10%
ACR50	67%	5%	79%	5%
ACR70	61%	2%	67%	2%
ACR90	42%	0%	47%	2%
ACR100	33%	0%	33%	2%
Inactive disease	33%	0%	30%	0%
Treatment difference for all ACR scores was significant ($p \leq 0.0001$)				

Results for the components of the adapted paediatric ACR which included systemic and arthritic components, were consistent with the overall ACR response results. At day 15, the median change from baseline in the number of joints with active arthritis and limited range of motion were -67% and -73% for Ilaris (N=43), respectively, compared to a median change of 0% and 0% for placebo (N=41). The mean change in patient pain score (0-100 mm visual analogue scale) at day 15 was -50.0 mm for Ilaris (N=43), as compared to +4.5 mm for placebo (N=25). The mean change in pain score among Ilaris treated patients was consistent at day 29.

Study G2301
Study G2301 was a randomised, double-blind, placebo-controlled withdrawal study of flare prevention by Ilaris. The study consisted of two parts with two independent primary endpoints (successful steroid taper and time to flare). In part I (open label) 177 patients were enrolled and received 4 mg/kg (up to 300 mg) Ilaris administered every 4 weeks for up to 32 weeks. Patients in part II (double-blind) received either Ilaris 4 mg/kg or placebo every 4 weeks until 37 flare events occurred.

Corticosteroid dose tapering:
Of the total 128 patients who entered part I taking corticosteroids, 92 attempted corticosteroid tapering. Fifty-seven (62%) of the 92 patients who attempted to taper were able to successfully taper their corticosteroid dose and 42 (46%) discontinued corticosteroids.

Time to flare:
Patients taking Ilaris in part II had a 64% reduced risk of a flare event as compared to the placebo group (hazard ratio of 0.36; 95% CI: 0.17 to 0.75; p=0.0032). Sixty-three of the 100 patients entering part II, whether assigned to placebo or canakinumab, did not experience a flare over the observation period (up to a maximum of 80 weeks).

Health-related and quality of life outcomes in studies G2305 and G2301
Treatment with Ilaris resulted in clinically relevant improvements in patients' physical function and quality of life. In study G2305, the Childhood Health Assessment Questionnaire Least Squares means improvement was 0.69 for Ilaris vs placebo representing 3.6 times the minimal clinically important difference of 0.19 (p=0.0002). The median improvement from baseline to end of part I of study G2301 was 0.88 (79%). Statistically significant improvements in the Child Health Questionnaire-PF50 scores

were reported for Ilaris vs placebo in study G2305 (physical p=0.0012; psychosocial well-being p=0.0017).

Pooled Efficacy Analysis
Data from the first 12 weeks of Ilaris treatment from studies G2305, G2301 and the extension study were pooled to assess maintenance of efficacy. These data showed similar improvements from baseline to week 12 in the adapted paediatric ACR responses and its components to those observed in the placebo controlled study (G2305). At week 12, the adapted paediatric ACR30, 50, 70, 90 and 100 responses were: 70%, 69%, 61%, 49% and 30%, respectively and 28% of patients had inactive disease (N=178).

The efficacy observed in the studies G2305 and G2301 was maintained in the ongoing, open-label long-term extension study (data available through median of 49 weeks of follow-up). In this study, 25 patients who had a strong ACR response for a minimum of 5 months reduced their Ilaris dose to 2 mg/kg every 4 weeks and maintained a paediatric ACR100 response throughout the time the reduced dose was given (median 32 weeks, 8-124 weeks).

Although limited, evidence from the clinical trials suggests that patients not responding to tocilizumab or anakinra, may respond to canakinumab.

SJIA in young adults and AOSD
Efficacy of Ilaris in a subset of young adult SJIA patients aged 16 to 20 years was consistent with the efficacy observed for patients less than 16 years of age. The efficacy profile in AOSD patients is expected to be similar to SJIA patients based on literature reports.

Gouty arthritis
The efficacy of Ilaris for the treatment of acute gouty arthritis attacks was demonstrated in two multicentre, randomised, double-blind, active-controlled studies in patients with frequent gouty arthritis (≥ 3 attacks in the previous 12 months) unable to use NSAIDs or colchicine (due to contraindication, intolerance or lack of efficacy). The studies were 12 weeks followed by 12-week double-blind extension. A total of 225 patients were treated with subcutaneous Ilaris 150 mg and 229 patients were treated with intramuscular triamcinolone acetonide (TA) 40 mg at study entry, and when experiencing a new attack thereafter. The mean number of gouty arthritis attacks in the previous 12 months was 6.5. Over 85% of patients had comorbidity, including hypertension (60%), diabetes (15%), ischaemic heart disease (12%), and stage ≥ 3 chronic kidney disease (25%). Approximately one-third of the patients enrolled (76 [33.8%] in the Ilaris group and 84 [36.7%] in the triamcinolone acetonide group) had documented inability (intolerance, contraindication or lack of response) to use both NSAIDs and colchicine. Concomitant treatment with ULTs was reported by 42% of patients at entry.

The co-primary endpoints were: (i) gouty arthritis pain intensity (visual analogue scale, VAS) at 72 hours post-dose, and (ii) time to first new gouty arthritis attack.

For the overall study population, pain intensity was statistically significantly lower for Ilaris 150 mg compared with triamcinolone acetonide at 72 hours. Ilaris also reduced the risk of subsequent attacks (see Table 4).

Efficacy results in a subgroup of patients unable to use both NSAIDs and colchicine and who were on ULT, failed ULT or had a contraindication to ULT (N=101) were consistent with the overall study population with a statistically significant difference compared to triamcinolone acetonide in pain intensity at 72 hours (-10.2 mm, p=0.0208) and in reduction of risk of subsequent attacks (Hazard ratio 0.39, p=0.0047 at 24 weeks).

Efficacy results for a more stringent subgroup limited to current users of ULT (N=62) are presented in Table 4. Treatment with Ilaris induced a reduction of pain and reduced the risk of subsequent attacks in patients using ULT and unable to use both NSAIDs and colchicine, although the observed treatment

difference compared to triamcinolone acetonide was less pronounced than with the overall study population.

Table 4 Efficacy for the overall study population and in a subgroup of patients currently using ULT and unable to use both NSAIDs and colchicine

Efficacy endpoint	Overall study population; N=454	Unable to use both NSAIDs and colchicine; on ULT N=62
Treatment of gouty arthritis attacks as measured by pain intensity (VAS) at 72 h		
Least Squares mean estimated difference to triamcinolone acetonide	-10.7	-3.8
CI	(-15.4, -6.0)	(-16.7, 9.1)
p-value, 1-sided	p < 0.0001*	p=0.2798
Risk reduction of subsequent gouty arthritis attacks as measured by time to first new flare (24 weeks)		
Hazard ratio to triamcinolone acetonide	0.44	0.71
CI	(0.32, 0.60)	(0.29, 1.77)
p-value, 1-sided	p < 0.0001*	p=0.2337
* Denotes significant p-value ≤ 0.025		

Safety results showed an increased incidence of adverse events for canakinumab compared to triamcinolone acetonide, with 66% vs 53% of patients reporting any adverse event and 20% vs 10% of patients reporting an infection adverse event over 24 weeks.

Elderly population
Overall, the efficacy, safety and tolerability profile of Ilaris in elderly patients ≥ 65 years of age was comparable to patients < 65 years of age.

Patients on urate lowering therapy (ULT)
In clinical studies, Ilaris has been safely administered with ULT. In the overall study population, patients on ULT had a less pronounced treatment difference in both pain reduction and reduction in the risk of subsequent gouty arthritis attacks compared to patients not on ULT.

Immunogenicity
Antibodies against Ilaris were observed in approximately 1.5%, 3% and 2% of the patients treated with Ilaris for CAPS, SJIA and gouty arthritis, respectively. No neutralising antibodies were detected. No apparent correlation of antibody development to clinical response or adverse events was observed.

This medicinal product has been authorised for CAPS under "Exceptional Circumstances". This means that due to the rarity of the disease it has not been possible to obtain complete information on this medicinal product. The European Medicines Agency will review any new information which may become available every year and this SmPC will be updated as necessary.

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with Ilaris in one or more subsets of the paediatric population in Cryopyrin Associated Periodic Syndromes (CAPS) and Juvenile Idiopathic Arthritis (see section 4.2 for information on paediatric use).

The European Medicines Agency has waived the obligation to submit the results of studies with Ilaris in all subsets of the paediatric population in gouty arthritis (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

CAPS

Absorption

The peak serum canakinumab concentration (C_{max}) occurred approximately 7 days following single subcutaneous administration of 150 mg in adult CAPS patients. The mean terminal half-life was 26 days. Mean values for C_{max} and AUC_{inf} after a single subcutaneous dose of 150 mg in a typical adult CAPS patient (70 kg) were 15.9 µg/ml and 708 µg*d/ml. The absolute bioavailability of subcutaneously administered canakinumab was estimated to be 66%. Exposure parameters (such as AUC and C_{max}) increased in proportion to dose over the dose range of 0.30 to 10.0 mg/kg given as intravenous infusion or from 150 to 600 mg as subcutaneous injection. Predicted steady-state exposure values ($C_{min,ss}$, $C_{max,ss}$, $AUC_{,ss,8w}$) after 150 mg subcutaneous administration (or 2 mg/kg, respectively) every 8 weeks were slightly higher in the weight category 40-70 kg (6.6 µg/ml, 24.3 µg/ml, 767 µg*d/ml) compared to the weight categories < 40 kg (4.0 µg/ml, 19.9 µg/ml, 566 µg*d/ml) and > 70 kg (4.6 µg/ml, 17.8 µg/ml, 545 µg*d/ml). The expected accumulation ratio was 1.3-fold following 6 months of subcutaneous administration of 150 mg canakinumab every 8 weeks.

Distribution

Canakinumab binds to serum IL-1 beta. The distribution volume (V_{ss}) of canakinumab varied according to body weight. It was estimated to be 6.2 litres in a CAPS patient of body weight 70 kg.

Elimination

The apparent clearance (CL/F) of canakinumab increases with body weight. It was estimated to be 0.17 l/d in a CAPS patient of body weight 70 kg and 0.11 l/d in a SJIA patient of body weight 33 kg. After accounting for body weight differences, no clinically significant differences in the pharmacokinetic properties of canakinumab were observed between CAPS and SJIA patients.

There was no indication of accelerated clearance or time-dependent change in the pharmacokinetic properties of canakinumab following repeated administration. No gender or age-related pharmacokinetic differences were observed after correction for body weight.

Still's Disease (AOSD and SJIA)

Bioavailability in SJIA patients has not been determined independently. Apparent clearance per kg body weight (CL/F per kg) was comparable between the SJIA and CAPS population (0.004 l/d per kg). The apparent volume of distribution per kg (V/F per kg) was 0.14 l/kg.

After repeated administration of 4 mg/kg every 4 weeks the accumulation ratio of canakinumab was 1.6 fold in SJIA patients. Steady state was reached after 110 days. The overall predicted mean (±SD) for $C_{min,ss}$, $C_{max,ss}$ and $AUC_{,ss4w}$ were 14.7±8.8 µg/ml, 36.5 ± 14.9 µg/ml and 696.1 ± 326.5 µg*d/ml, respectively.

The AUC_{ss4w} in each age group was 692, 615, 707 and 742 µg*d/ml for 2-3, 4-5, 6-11, and 12-19 years old, respectively. When stratified by weight, a lower (30-40%) median of exposure for $C_{min,ss}$ (11.4 vs 19 µg/ml) and AUC_{ss} (594 vs 880 µg*d/ml) for the lower bodyweight category (≤ 40 kg) vs the higher bodyweight category (> 40 kg) was observed.

Based on the population pharmacokinetic modelling analysis, the pharmacokinetics of canakinumab in young adult SJIA patients aged 16 to 20 years were similar to those in patients less than 16 years of age. Predicted canakinumab steady state exposures at a dose level of 4 mg/kg (maximum 300 mg) in patients over the age of 20 years were comparable to those in SJIA patients younger than 20 years of age.

Gouty arthritis population

Bioavailability in gouty arthritis patients has not been determined independently. Apparent clearance per kg body weight (CL/F per kg) was comparable between the gouty arthritis and CAPS population (0.004 l/d/kg). Mean exposure in a typical gouty arthritis patient (93 kg) after a single subcutaneous 150 mg dose (C_{max}: 10.8 µg/ml and AUC_{inf}: 495 µg*d/ml) was lower than in a typical 70 kg CAPS

patient (15.9 µg/ml and 708 µg*d/ml). This is consistent with the observed increase in CL/F with body weight.

The expected accumulation ratio was 1.1-fold following subcutaneous administration of 150 mg canakinumab every 12 weeks.

Paediatric population
Peak concentrations of canakinumab occurred between 2 to 7 days (T_{max}) following single subcutaneous administration of canakinumab 150 mg or 2 mg/kg in paediatric patients 4 years of age and older. The terminal half-life ranged from 22.9 to 25.7 days, similar to the pharmacokinetic properties observed in adults. Based on the population pharmacokinetic modelling analysis, the pharmacokinetics of canakinumab in children aged 2 to < 4 years were similar to those in patients 4 years of age and older. Subcutaneous absorption rate was estimated to decrease with age and appeared to be fastest in the youngest patients. Accordingly, T_{max} was shorter (3.6 days) in younger SJIA patients (2-3 years) compared to older SJIA patients (12-19 years; T_{max} 6 days). Bioavailability (AUC_{ss}) was not affected.

An additional pharmacokinetics analysis showed that the pharmacokinetics of canakinumab in 6 paediatric CAPS patients under the age of 2 years were similar to the pharmacokinetics in paediatric patients 2-4 years of age. Based on the population pharmacokinetic modelling analysis, the expected exposures after a dose of 2 mg/kg were comparable across the CAPS paediatric age groups, but were approximately 40% lower in paediatric patients of very low body weight (e.g., 10 kg) than in adult patients (150 mg dose). This is consistent with the observations of higher exposure in higher body weight groups in CAPS patients.

Pharmacokinetic properties are similar in CAPS and SJIA paediatric populations.

Elderly population
No change in pharmacokinetic parameters based on clearance or volume of distribution were observed between elderly patients and adult patients < 65 years of age.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on cross-reactivity, repeated dose, immunotoxicity, reproductive and juvenile toxicity studies performed with canakinumab or a murine anti-murine IL-1 beta antibody.

Since canakinumab binds to marmoset (*C. jacchus*) and human IL-1 beta with a similar affinity, the safety of canakinumab has been studied in the marmoset. No undesirable effects of canakinumab were seen following twice weekly administration to marmosets for up to 26 weeks or in an embryofoetal developmental toxicity study in pregnant marmosets. Plasma concentrations that are well tolerated in animals are in excess of at least 42-fold (C_{max}) and 78-fold (C_{avg}) the plasma concentrations in paediatric CAPS patients (body weight 10 kg) treated with clinical doses of canakinumab up to 8 mg/kg subcutaneously every 8 weeks. Plasma concentrations that are well tolerated in animals exceed at least 62-fold (C_{max}) and 104-fold (C_{avg}) the plasma concentrations in paediatric SJIA patients, treated with up to 4 mg/kg via the subcutaneous route every 4 weeks. In addition, no antibodies to canakinumab were detected in these studies. No non-specific tissue cross-reactivity was demonstrated when canakinumab was applied to normal human tissues.

Formal carcinogenicity studies have not been conducted with canakinumab.

In an embryofoetal development study in marmosets canakinumab showed no maternal toxicity, embryotoxicity or teratogenicity when administered throughout organogenesis.

No undesirable effects of a murine anti-murine IL-1 beta antibody were seen in a complete set of reproductive and juvenile studies in mice. Anti-murine IL-1 beta did not elicit adverse events on foetal or neonatal growth when administered throughout late gestation, delivery and nursing (see section 4.6).

The high dose used in these studies was in excess of the maximally effective dose in terms of IL-1 beta suppression and activity.

An immunotoxicology study in mice with a murine anti-murine IL-1 beta antibody showed that neutralising IL-1 beta has no effects on immune parameters and caused no impairment of immune function in mice.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder for solution for injection:
Sucrose
Histidine
Histidine hydrochloride monohydrate
Polysorbate 80

Solvent:
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years.

After reconstitution, from a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).
Do not freeze.
Store in the original package in order to protect from light.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Powder: 150 mg of powder for solution for injection in a 6 ml vial (type I glass) with a stopper (coated chlorobutyl rubber) and flip-off cap (aluminium/plastic disc).
Solvent: 5 ml of water for injections in a 6 ml vial (type I glass) with a stopper (fluoropolymer-coated chlorobutyl rubber) and flip-off cap (aluminium/plastic disc).

One Ilaris injection kit contains 1 vial of powder for solution for injection, 1 vial of solvent,1 injection syringe of 1 ml, 1 safety needle, 2 vial adapters and 4 cleansing swabs.

6.6 Special precautions for disposal and other handling

Ilaris 150 mg powder and solvent for solution for injection is supplied in a single-use vial for individual use. Only use the contents provided in the Ilaris injection kit. Any unused medicinal product or waste material or syringe should be disposed of in accordance with local requirements.

Instructions for reconstitution
Using aseptic technique, attach the vial adapters to the Ilaris and solvent vials. Transfer 1.0 ml of air into the solvent vial, then withdraw 1.0 ml of water for injections from the solvent vial using the syringe provided in the kit. Reconstitute the content of Ilaris vial at room temperature (typically 15°C to 25°C) by slowly injecting 1.0 ml of water for injections withdrawn from the solvent vial. Swirl the vial slowly at an angle of about 45° for approximately 1 minute and allow to stand for about 5 minutes. Then gently turn the vial upside down and back again ten times. Allow to stand for about 15 minutes at room temperature. Do not shake. Do not use if particles are present in the solution.

Tap the side of the vial to remove any residual liquid from the stopper. The solution should be free of visible particles and not cloudy. The solution should be colourless or may have a slight brownish-yellow tint. If the solution has a distinctly brown discolouration it should not be used. If not used immediately after reconstitution, the solution should be kept at 2°C to 8°C and used within 24 hours.

Instructions for administration
Carefully withdraw the required volume depending on the dose to be administered (0.2 ml to 1.0 ml) and subcutaneously inject using the safety needle provided in the kit.

The following are suitable injection sites: upper thigh, abdomen, upper arm or buttocks. Select a different injection site each time you inject to avoid soreness. Broken skin and areas which are bruised or covered by a rash should be avoided. Injection into scar tissue should be avoided as this may result in insufficient exposure to Ilaris.

Disposal
The residual volume should be discarded immediately after the injection. Patients or their caregivers should be instructed on the appropriate procedure for disposal of the vials, syringes and needles in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/564/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 October 2009
Date of latest renewal: 19 June 2014

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Novartis Pharma S.A.S.
Centre de Biotechnologie
8, rue de l'Industrie
68330 Huningue
France

Name and address of the manufacturer responsible for batch release

Novartis Pharma GmbH
Roonstrasse 25
D-90429 Nürnberg
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached

- **Additional risk minimisation measures**

The Marketing Authorisation Holder (MAH) shall ensure that, prior to launch, all physicians who are expected to prescribe/use Ilaris are provided with a physician information pack containing the following:

- The Summary of Product Characteristics
- Physician information
- Patient Alert Card

The physician information should contain the following key messages:

- The risk of serious infections, including opportunistic bacterial, viral and fungal infections in patients treated with Ilaris;
- The risk of acute injection-related reactions;
- For CAPS patients: the need to instruct patients on proper techniques for self-administration when the patient is willing and capable to do so, and guidance for Health Care Professionals on how to report administration errors;
- The identified or potential risk of immunogenicity that might lead to immune-mediated symptoms. For gouty arthritis patients: highlighting that intermittent therapy or re-exposure after a long treatment-free interval may be associated with an enhanced immune response (or loss of immune tolerance) to Ilaris and thus re-treated patients must be considered at risk of hypersensitivity reactions;
- For chronic therapy in CAPS: the need for Health Care Professionals to perform an annual clinical assessment of patients regarding a potential increased risk for the development of malignancies;
- As treatment with Ilaris should not be initiated in patients with neutropenia, the need to measure neutrophil counts prior to initiating treatment and again after 1 to 2 months. For chronic therapy in CAPS patients or repeated therapy in gouty arthritis patients, it is recommended to assess neutrophil counts periodically during treatment;
- For SJIA patients, the need for Health Care Professionals to be attentive to symptoms of infection or worsening of SJIA, as these are known triggers for macrophage activation syndrome (MAS) which is a known, life-threatening disorder that may develop in patients with rheumatic conditions, in particular SJIA patients. If MAS occurs, or is suspected, evaluation and treatment should be started as early as possible;
- The need to monitor patients for changes in their lipid profiles;
- The unknown safety of Ilaris in pregnant and lactating women, thus the need for physicians to discuss this risk with patients if they become or plan to become pregnant;
- The proper patient management as regards the interaction with vaccination;
- The possibility to include patients in the registry study to facilitate the collection of long term efficacy and safety data;
- The role and use of patient alert card.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

This being an approval under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall conduct, within the stated timeframe, the following measures:

Area	Description	Due date
Clinical SO 1	The MAH is requested to provide reports on the ß-Confident registry (CACZ885D2401), which was designed to provide data on long-term safety and effectiveness of Ilaris treatment in paediatric and adult CAPS patients in routine clinical practice. In these reports the MAH is requested to specifically assess cases for whom there is a loss of efficacy (patients reported to have	Annually within the annual re-assessment

	discontinued Ilaris for lack-of-therapeutic response) to determine whether this is due to changes over time in PK/PD or antibody development (where data is available) or in whom a dose adjustment has led to improved therapeutic response (patients with a dose up titration without discontinuation for lack-of-therapeutic response). The MAH is required to provide updates on the recruitment rates and any intermediary results annually within the annual re-assessment. The patients should be included in the Registry until both following conditions are met: 5 years recruitment period and 200 patients included.	

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

UNIT PACK CARTON (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Ilaris 150 mg powder for solution for injection
Canakinumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains 150 mg canakinumab.

3. LIST OF EXCIPIENTS

Also contains: sucrose, histidine, histidine hydrochloride monohydrate, polysorbate 80.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for injection.
1 vial of powder.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Single use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

After reconstitution, from a microbiological point of view immediate use is recommended. However in-use stability has been demonstrated for 24 hours at 2°C-8°C.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/564/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ilaris 150 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACK (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Ilaris 150 mg powder for solution for injection
Canakinumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains 150 mg canakinumab.

3. LIST OF EXCIPIENTS

Also contains: sucrose, histidine, histidine hydrochloride monohydrate, polysorbate 80.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for injection.
Multipack comprising 4 intermediate packs, each containing 1 vial of powder.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Single use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

After reconstitution, from a microbiological point of view immediate use is recommended. However in-use stability has been demonstrated for 24 hours at 2°C-8°C.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/564/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ilaris 150 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Ilaris 150 mg powder for solution for injection
Canakinumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains 150 mg canakinumab.

3. LIST OF EXCIPIENTS

Also contains: sucrose, histidine, histidine hydrochloride monohydrate, polysorbate 80.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for injection.
Component of a multipack comprising 4 intermediate packs, each containing 1 vial.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Single use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

After reconstitution, from a microbiological point of view immediate use is recommended. However in-use stability has been demonstrated for 24 hours at 2°C-8°C.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/564/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ilaris 150 mg

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Ilaris 150 mg powder for solution for injection
Canakinumab
Subcutaneous use after reconstitution

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

150 mg

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

UNIT PACK CARTON (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Ilaris 150 mg powder and solvent for solution for injection
Canakinumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains 150 mg canakinumab.

3. LIST OF EXCIPIENTS

Powder: sucrose, histidine, histidine hydrochloride monohydrate, polysorbate 80.
Solvent: water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection.
1 vial of powder + 1 vial of solvent + 1 ml injection syringe + 1 safety needle + 2 vial adapters + 4 cleansing swabs.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Single use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

After reconstitution, from a microbiological point of view immediate use is recommended. However in-use stability has been demonstrated for 24 hours at 2°C -8°C.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/564/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ilaris 150 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INNER LID OF UNIT PACK CARTON

1. OTHER

Contents



1 vial of powder



1 vial of solvent



1 ml injection syringe



1 safety needle



2 vial adapters



4 cleansing swabs

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL - POWDER

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Ilaris 150 mg powder for solution for injection
Canakinumab
Subcutaneous use after reconstitution

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

150 mg

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL – SOLVENT

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Solvent for Ilaris
Water for injections

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 ml

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Ilaris 150 mg powder for solution for injection
Canakinumab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Ilaris is and what it is used for
2. What you need to know before you use Ilaris
3. How to use Ilaris
4. Possible side effects
5. How to store Ilaris
6. Contents of the pack and other information

1. What Ilaris is and what it is used for

What Ilaris is
Ilaris contains the active substance canakinumab, a monoclonal antibody that belongs to the pharmacotherapeutic group of interleukin inhibitors. It blocks the activity of a substance called interleukin-1 beta (IL-1 beta) in the body, which is present at increased levels in inflammatory diseases such as Cryopyrin-Associated Periodic Syndromes (CAPS), Still's disease including Adult-Onset Still's Disease (AOSD) and Systemic Juvenile Idiopathic Arthritis (SJIA) and gouty arthritis.
Ilaris is used for treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), Still's disease including Adult-Onset Still's Disease (AOSD) and Systemic Juvenile Idiopathic Arthritis (SJIA) and gouty arthritis.

What Ilaris is used for
Cryopyrin-Associated Periodic Syndromes
Ilaris is used in adults, adolescents and children aged 2 years and older with body weight of 7.5 kg or above to treat the following auto-inflammatory diseases, which are collectively known as Cryopyrin-Associated Periodic Syndromes (CAPS):
- Muckle-Wells Syndrome (MWS),
- Neonatal-Onset Multisystem Inflammatory Disease (NOMID), also called Chronic Infantile Neurological, Cutaneous, Articular Syndrome (CINCA),
- Severe forms of Familial Cold Autoinflammatory Syndrome (FCAS) / Familial Cold Urticaria (FCU) presenting with signs and symptoms beyond cold-induced urticarial skin rash.

In patients with CAPS, the body produces excessive amounts of IL-1 beta. This may lead to symptoms such as fever, headache, fatigue, skin rash, or painful joints and muscles. By blocking the activity of IL-1 beta, Ilaris may lead to an improvement in these symptoms.

Still's Disease
Ilaris is used in adults, adolescents and children to treat active Still's disease including Adult-Onset Still's Disease (AOSD) and Systemic Juvenile Idiopathic Arthritis (SJIA) in patients aged 2 years and older if other treatments have not worked well enough. Ilaris can be used alone or in combination with methotrexate.

Still's disease including AOSD and SJIA is an inflammatory disease that can cause pain, swelling and inflammation of one or more joints, as well as rash and fever. A pro-inflammatory protein called IL-1 beta plays an important role in Still's disease inflammatory processes and by blocking the activity of IL-1 beta Ilaris may lead to an improvement in the signs and symptoms of Still's disease.

Gouty arthritis
Ilaris is used in adults to treat the symptoms of frequent gouty arthritis attacks if other treatments have not worked well enough.

Gouty arthritis is caused by the deposition of a chemical called urate crystals in the body. These crystals cause excessive production of IL-1 beta, which in turn can lead to sudden, severe pain, redness, warmth and swelling in a joint (known as a gouty arthritis attack). By blocking the activity of IL-1 beta, Ilaris may lead to an improvement in these symptoms.

If you have any questions about how Ilaris works or why this medicine has been prescribed for you, ask your doctor, pharmacist or nurse.

2. What you need to know before you use Ilaris

Do not use Ilaris
- if you are allergic to canakinumab or any of the other ingredients of this medicine (listed in section 6).
- if you have, or suspect you have, an active, severe infection.

Warning and precautions
Talk to your doctor before using Ilaris if any of the following applies to you:
- if you currently have an infection or if you have had repeated infections or a condition such as a known low level of white blood cells which makes you more likely to get infections.
- if you have or have ever had tuberculosis or direct contact with a person with an active tuberculosis infection. Your doctor may also check whether you have tuberculosis using a specific test.
- if you have signs of an allergic reaction such as difficulty breathing or swallowing, nausea, dizziness, skin rash, itching, hives, palpitations or low blood pressure.
- if you have signs of a liver disorder such as yellow skin and eyes, nausea, loss of appetite, dark-coloured urine and light-coloured stools.
- if you need to have any vaccinations. You are advised to avoid being vaccinated with a type of vaccine called a live vaccine while being treated with Ilaris (see also "Other medicines (including vaccines) and Ilaris").

<u>Still's Disease</u>
- Patients with Still's disease may develop a condition called macrophage activation syndrome (MAS), which can be life-threatening. Your doctor will monitor you for potential triggering factors of MAS that include infections and re-activation of the underlying Still's disease (flare).

Children and adolescents
- CAPS and SJIA: Ilaris can be used in children aged 2 years and older.
- Gouty arthritis: Ilaris is not recommended for children or adolescents under 18 years of age.

Other medicines (including vaccines) and Ilaris
Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines.
- Live vaccines: you are advised to avoid being vaccinated with a type of vaccine called a live vaccine while being treated with Ilaris. Your doctor may want to check your vaccination history and give you any vaccinations that you have missed before you start treatment with Ilaris. If you need to be given a live vaccine after starting treatment with Ilaris, you are advised to wait for at least 3 months after the last Ilaris injection and before the next injection.
- Medicines called tumour necrosis factor (TNF) inhibitors, such as etanercept, adalimumab or infliximab. These are used mainly in rheumatic and autoimmune diseases. They should not be used with Ilaris because this may increase the risk of infections.

Pregnancy and breast-feeding
- Ilaris has not been studied in pregnant women. You are advised to avoid becoming pregnant and must use adequate contraception while using Ilaris and for at least 3 months after the last Ilaris treatment. It is important to tell your doctor if you are pregnant, if you think you may be pregnant or are planning to have a baby. Your doctor will discuss with you the potential risk of taking Ilaris during pregnancy.
- If you received canakinumab while you were pregnant, it is important that you inform the baby's doctor or nurse before any vaccinations are given to your baby. Your baby should not receive live vaccines until at least 16 weeks after you received your last dose of canakinumab before giving birth.
- It is not known whether Ilaris passes into human milk. Your doctor will discuss with you the potential risks of taking Ilaris before breast-feeding.

Driving and using machines
Ilaris treatment may give you a spinning sensation (dizziness/vertigo) or intense tiredness (asthenia). This may affect your ability to drive or use tools or machines. If you feel a spinning sensation or feel tired, do not drive or use any tools or machines until you are feeling normal again.

3. How to use Ilaris

If you have CAPS or Still's disease (AOSD or SJIA), you may inject yourself with Ilaris after proper training, or a caregiver may inject it for you.

Always use this medicine exactly as your doctor has told you. Check with your doctor, pharmacist or nurse if you are not sure.

If you have gouty arthritis, your treatment will be overseen by a doctor with specialist training. Ilaris should be injected by a healthcare professional only.

Keep your doctor informed of your condition and any symptoms before you use or are given Ilaris (see section 2). Your doctor may decide to delay or interrupt your treatment, but only if necessary.

Ilaris is intended for subcutaneous use. This means that it is injected through a short needle into the fatty tissue just under the skin.

How much Ilaris to use
Cryopyrin-Associated Periodic Syndromes
The recommended starting dose of Ilaris is:
Adults, adolescents and children aged 4 years or more
- 150 mg for patients with body weight more than 40 kg
- 2 mg/kg for patients with body weight of 15 kg or more, up to a maximum of 40 kg
- 4 mg/kg for patients with body weight of 7.5 kg or more, but below 15 kg

Children aged 2 or 3 years
- 4 mg/kg for patients with body weight of 7.5 kg or more

Ilaris is injected every 8 weeks as a single dose.

If you have not responded sufficiently to treatment after 7 days, your doctor may consider giving you a repeat dose of 150 mg or 2 mg/kg. If you respond sufficiently to this, your treatment will continue with this higher dose of 300 mg or 4 mg/kg every 8 weeks. If you do not respond sufficiently to the repeat dose, a third dose of Ilaris at 300 mg or 4 mg/kg can be considered, and if you respond sufficiently to that, your treatment may continue at 600 mg and 8 mg/kg every 8 weeks.

For patients given a starting dose of 4 mg/kg who have not responded sufficiently after 7 days, a second dose of 4 mg/kg can be considered. If the patient responds sufficiently to this, treatment may be continued with 8 mg/kg every 8 weeks.

Still's Disease (AOSD and SJIA)
The recommended dose of Ilaris for patients with Still's disease (AOSD or SJIA) with body weight of 7.5 kg and above is 4 mg/kg (up to a maximum of 300 mg). Ilaris is given as an injection under the skin every 4 weeks.

Gouty arthritis
Your doctor will discuss with you the need to start or adjust a urate lowering therapy to lower the uric acid level in your blood.

The recommended dose of Ilaris for adult gouty arthritis patients is 150 mg given as a single dose at the time of a gouty arthritis attack.

If you need another treatment with Ilaris, and got relief from the last dose, you must wait at least 12 weeks before the next dose.

Injecting Ilaris yourself or injecting a child with Ilaris
If you have CAPS or Still's disease (AOSD or SJIA), patients or caregivers of child patients may administer Ilaris injections themselves after proper training in the correct injection technique.
- The patient or caregiver and the doctor should decide together who will administer the Ilaris injections.
- The doctor or nurse will demonstrate how to administer Ilaris injections.
- Do not try to administer an injection yourself if you have not been properly trained or if you are not sure how to do it.
- Ilaris 150 mg powder for solution for injection is supplied in a single-use vial for individual use.
- Never re-use the left-over solution.

For instructions on how to administer Ilaris injections, please read the section "Instructions for use" at the end of this leaflet. If you have any questions, talk to your doctor, pharmacist or nurse.

How long to use Ilaris
- If you have CAPS or Still's disease (AOSD or SJIA), you should continue using Ilaris for as long as the doctor tells you.

- If you have a gouty arthritis attack, you will be given a single dose of Ilaris. If you experience a new attack, your doctor may consider giving you a new dose of Ilaris but not earlier than 12 weeks from the previous dose.

If you use more Ilaris than you should
If you accidentally inject more Ilaris than the recommended dose, it is unlikely to be serious, but you should inform your doctor, pharmacist or nurse as soon as possible.

If you inject Ilaris sooner than you should
- In CAPS, you should not inject Ilaris earlier than 8 weeks after the last dose, unless your doctor tells you to.
- In Still's disease (AOSD or SJIA), you should not inject Ilaris earlier than 4 weeks after the last dose.

If you accidentally inject Ilaris sooner than you should, tell your doctor, pharmacist or nurse as soon as possible.

If you forget to use Ilaris
If you have CAPS or Still's disease (AOSD or SJIA) and have forgotten to inject a dose of Ilaris, inject the next dose as soon as you remember. Then talk to the doctor to discuss when you should inject the next dose. You should then continue with injections at the recommended intervals as before.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Most of the side effects are mild to moderate and will generally disappear a few days to a few weeks after treatment.

Some side effects could be serious. Tell your doctor immediately, if you notice any of the side effects below:
- Fever lasting longer than 3 days or any other symptoms that might be due to an infection. These include shivering, chills, malaise, loss of appetite, body aches, typically in connection with a sudden onset of illness, sore throat or mouth ulcers, cough, phlegm, chest pain, difficulty breathing, ear pain, prolonged headache or localised redness, warmth or swelling of your skin or inflammation of connective tissue (cellulitis). These symptoms could be due to an infection caused by low levels of white blood cells (called leucopenia or neutropenia). Your doctor may check your blood regularly if considered necessary.
- Allergic reactions with rash and itching and possibly also hives, difficulty breathing or swallowing, dizziness, unusual awareness of your heart beat (palpitations) or low blood pressure.

Other side effects of Ilaris include:
Very common (may affect more than 1 in 10 people):
- Sore throat, runny nose, blocked nose, sneezing, feeling of pressure or pain in the cheeks and/or forehead with or without fever (nasopharyngitis, pharyngitis, rhinitis, sinusitis).
- Combination of sore throat, fever, swollen or red tonsils, cough, difficulty to swallow and headache (tonsilitis), reported less frequently in gouty arthritis patients.
- Painful and frequent urination with or without fever (urinary tract infection).
- Drop in levels of blood platelets (called thrombocytopenia).
- Stomach pain and feeling sick (gastroenteritis).
- Abdominal pain.
- Pain in muscles, bones or joints.
- Abnormal kidney function test results (creatinine renal clearance decreased, proteinuria).
- Injection site reaction (such as redness, swelling, warmth and itching).

Common (may affect up to 1 in 10 people):
- Abnormal levels of triglycerides in your blood (lipid metabolism disorder).
- Abnormal liver function test results (transaminases increased).
- High level of bilirubin in the blood, with or without yellow skin and eyes (hyperbilirubinaemia).
- Feeling dizzy, spinning sensation (vertigo).
- Feeling weak or very tired (asthenia).
- Back pain.

Uncommon (may affect up to 1 in 100 people):
– Heartburn (gastro-oesophageal reflux).

Not known (frequency cannot be estimated from the available data):
– Being sick (vomiting).
– Increases in blood uric acid levels were observed in studies on gouty arthritis patients flaring.
– Prolonged fever (i.e. fever lasting longer than three days) or any other symptoms possibly related to an infection, such as prolonged cough, phlegm, chest pain, blood in sputum (saliva and phlegm that is coughed up), difficulty breathing, ear pain, prolonged headache or localised redness, warmth or swelling of your skin. These may be symptoms of a typical infection or one that may be more serious (opportunistic infections).

Tell your doctor or your child's doctor immediately if you notice any of these symptoms.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Ilaris

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and carton. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C - 8°C).
Do not freeze.
Store in the original package in order to protect from light.

After reconstitution, from a microbiological point of view, the product should be used immediately. However, chemical and physical in-use stability has been demonstrated for 24 hours at 2°C - 8°C.

Do not use Ilaris if you notice that the solution is not clear to opalescent or contains particles.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Ilaris contains
– The active substance is canakinumab. One vial of powder contains 150 mg canakinumab. After reconstitution, each ml of solution contains 150 mg canakinumab.
– The other ingredients are: sucrose, histidine, histidine hydrochloride monohydrate, polysorbate 80.

What Ilaris looks like and contents of the pack
– Ilaris is supplied as a powder for solution for injection in a 150 mg glass vial.
– The powder is white.
– Ilaris is available in packs containing one vial or multipacks comprising four intermediate packs, each containing one vial. Not all pack sizes may be marketed in your country.

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Manufacturer
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This leaflet was last revised in

This medicine has been authorised under "exceptional circumstances". This means that because of the rarity of this disease it has been impossible to get complete information on this medicine. The European Medicines Agency will review any new information on this medicine every year and this leaflet will be updated as necessary.

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu

INSTRUCTIONS FOR USE OF ILARIS POWDER FOR SOLUTION FOR INJECTION

Please note that the preparation of the injection at room temperature takes about 30 minutes.
See also section 3, "Injecting Ilaris yourself or injecting a child with Ilaris".

Read these instructions all the way through before beginning.

Essential preparation
- Find a clean place in which to prepare and administer the injection.
- Wash your hands with soap and water.
- Check the expiry dates on the vial and syringes. Do not use after the expiry date which is stated on the label and carton. The expiry date refers to the last day of that month.
- Always use new, unopened needles and syringes. Avoid touching the needles and the tops of the vials.

Gather together the necessary items
Included in the pack
One vial of Ilaris powder for solution for injection (keep refrigerated)

Not included in the pack
- one vial (or ampoule) of sterile water for injection ("water") (do not refrigerate)
- one 1.0 ml syringe
- one 18 G x 2 inch (50 mm) needle for reconstituting the powder ("transfer needle")
- one 27 G x 0.5 inch (13 mm) needle for injecting ("injection needle")
- alcohol swabs
- clean, dry cotton swabs
- an adhesive plaster
- a proper disposal container for used needles, syringe and vials (sharps container)

Mixing Ilaris

 1	1. Remove the protective caps from the Ilaris and water vials. Do not touch the vial stoppers. Clean the stoppers with the alcohol swab. 2. Open the wrappers containing the syringe and the transfer needle (bigger one) and attach the needle to the syringe. 3. Carefully remove the cap from the transfer needle and set the cap aside. Pull the plunger all the way down to the 1.0 ml mark, filling the syringe with air. Insert the needle into the water vial through the centre of the rubber stopper (Fig. 1). 4. Gently push the plunger all the way down until air is injected into the vial.
 2	5. Invert the vial and syringe assembly and bring to eye level (Fig. 2). 6. Make sure the tip of the transfer needle is covered by the water and slowly pull the syringe plunger down to slightly past the 1.0 ml mark. If you see bubbles in the syringe, remove bubbles as instructed by your healthcare provider or pharmacist. 7. Make sure 1.0 ml of water is in the syringe, then withdraw the needle from the vial. (There will be water remaining in the vial.)

 3	8. Insert the transfer needle through the centre of the stopper of the vial of Ilaris powder, taking care not to touch the needle or the stopper. Slowly inject 1.0 ml of water in to the vial containing the Ilaris powder (Fig. 3). 9. Carefully remove the syringe with the transfer needle from the vial and recap the needle as instructed by your healthcare provider or pharmacist.
 4a  4b	10. Without touching the rubber stopper, swirl (do not shake) the vial slowly at an angle of about 45 degrees for approximately 1 minute (Fig. 4a). Allow to stand for 5 minutes. 11. Now, gently turn the vial upside down and back again ten times, again taking care not to touch the rubber stopper (Fig. 4b). 12. Allow to stand for about 15 minutes at room temperature to obtain a clear to opalescent solution. Do not shake. Do not use if particles are present in the solution. 13. Make sure all of the solution is in the bottom of the vial. If drops remain on the stopper, tap the side of the vial to remove them. The solution should be clear to opalescent and free of visible particles. The solution should be colourless or may have a slight brownish-yellow tint. - If not used immediately after reconstitution, the solution should be stored in the refrigerator (2°C to 8°C) and used within 24 hours.

Preparing the injection

 5	14. Clean the rubber stopper of the vial containing the Ilaris solution with a new alcohol swab. 15. Uncap the transfer needle again. Pull the plunger of the syringe all the way down to the 1.0 ml mark, filling the syringe with air. Insert the syringe needle into the vial of Ilaris solution through the centre of the rubber stopper (Fig. 5). Gently push the plunger all the way down until air is injected into the vial. Do not inject air into the medicine.

 6a  6b	16. **Do not** invert the vial and syringe assembly (Fig. 6a). Insert the needle all the way into the vial until it reaches the bottom edge. 17. Tip the vial to ensure that the required amount of solution can be drawn into the syringe (Fig. 6b). NOTE: The required amount depends on the dose to be administered (0.2 ml to 1.0 ml). Your healthcare provider will instruct you on the right amount for you. 18. Slowly pull the syringe plunger up to the correct mark (0.2 ml to 1.0 ml), filling the syringe with Ilaris solution. If there are air bubbles in the syringe, remove bubbles as instructed by your healthcare provider. Ensure that the correct amount of solution is in the syringe. 19. Remove the syringe and needle from the vial. (There may be solution remaining in the vial.) Recap the transfer needle as instructed by your healthcare provider or pharmacist. Remove the transfer needle from the syringe. Place the transfer needle in the sharps container. 20. Open the wrapper containing the injection needle and attach the needle to the syringe. Set the syringe aside.

Giving the injection

 7	21. Choose an injection site on the upper thigh, abdomen, upper arm or buttocks. Do not use an area that has a rash or broken skin, or is bruised or lumpy. Avoid injecting into scar-tissue as this may lead to insufficient exposure to canakinumab. Avoid injecting in to a vein. 22. Clean the injection site with a new alcohol swab. Allow the area to dry. Uncap the injection needle. 23. Gently pinch the skin up at the injection site. Hold the syringe at a 90-degree angle and in a single, smooth motion, push the needle straight down completely into the skin (Fig. 7).

 8	24. Keep the needle all the way in the skin while slowly pushing the syringe plunger down until the barrel is empty (Fig. 8). Release the pinched skin and pull the needle straight out. Dispose of the needle and syringe in the sharps container without recapping or removing the needle.

After the injection

 9	25. Do not rub the injection area. If bleeding occurs, apply a clean, dry cotton swab over the area, and press gently for 1 to 2 minutes, or until bleeding stops (Fig. 9). Then apply an adhesive plaster.
 10	26. Safely dispose of needles and syringe in the sharps container or as directed by your healthcare provider or pharmacist (Fig. 10). Never re-use syringes or needles. 27. Properly dispose of vials containing remaining water and Ilaris solution (if any) as directed by your healthcare provider or pharmacist. Any unused product or waste material should be disposed of in accordance with local requirements. Keep the sharps container out of reach of children. Dispose of it as directed by your healthcare provider or pharmacist.

Package leaflet: Information for the user

Ilaris 150 mg powder and solvent for solution for injection
Canakinumab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Ilaris is and what it is used for
2. What you need to know before you use Ilaris
3. How to use Ilaris
4. Possible side effects
5. How to store Ilaris
6. Contents of the pack and other information

1. What Ilaris is and what it is used for

What Ilaris is
Ilaris contains the active substance canakinumab, a monoclonal antibody that belongs to the pharmacotherapeutic group of interleukin inhibitors. It blocks the activity of a substance called interleukin-1 beta (IL-1 beta) in the body, which is present at increased levels in inflammatory diseases such as Cryopyrin-Associated Periodic Syndromes (CAPS), Still's disease including Adult-Onset Still's Disease (AOSD) and Systemic Juvenile Idiopathic Arthritis (SJIA) and gouty arthritis.
Ilaris is used for treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), Still's disease including Adult-Onset Still's Disease (AOSD) and Systemic Juvenile Idiopathic Arthritis (SJIA) and gouty arthritis.

What Ilaris is used for
Cryopyrin-Associated Periodic Syndromes
Ilaris is used in adults, adolescents and children aged 2 years and older with body weight of 7.5 kg or above to treat the following auto-inflammatory diseases, which are collectively known as Cryopyrin-Associated Periodic Syndromes (CAPS):
- Muckle-Wells Syndrome (MWS),
- Neonatal-Onset Multisystem Inflammatory Disease (NOMID), also called Chronic Infantile Neurological, Cutaneous, Articular Syndrome (CINCA),
- Severe forms of Familial Cold Autoinflammatory Syndrome (FCAS) / Familial Cold Urticaria (FCU) presenting with signs and symptoms beyond cold-induced urticarial skin rash.

In patients with CAPS, the body produces excessive amounts of IL-1 beta. This may lead to symptoms such as fever, headache, fatigue, skin rash, or painful joints and muscles. By blocking the activity of IL-1 beta, Ilaris may lead to an improvement in these symptoms.

Still's Disease
Ilaris is used in adults, adolescents and children to treat active Still's disease including Adult-Onset Still's Disease (AOSD) and Systemic Juvenile Idiopathic Arthritis (SJIA) in patients aged 2 years and older if other treatments have not worked well enough. Ilaris can be used alone or in combination with methotrexate.

Still's disease including AOSD and SJIA is an inflammatory disease that can cause pain, swelling and inflammation of one or more joints, as well as rash and fever. A pro-inflammatory protein called IL-1 beta plays an important role in Still's disease inflammatory processes and by blocking the activity of IL-1 beta Ilaris may lead to an improvement in the signs and symptoms of Still's disease.

Gouty arthritis
Ilaris is used in adults to treat the symptoms of frequent gouty arthritis attacks if other treatments have not worked well enough.

Gouty arthritis is caused by the deposition of a chemical called urate crystals in the body. These crystals cause excessive production of IL-1 beta, which in turn can lead to sudden, severe pain, redness, warmth and swelling in a joint (known as a gouty arthritis attack). By blocking the activity of IL-1 beta, Ilaris may lead to an improvement in these symptoms.

If you have any questions about how Ilaris works or why this medicine has been prescribed for you, ask your doctor, pharmacist or nurse.

2. What you need to know before you use Ilaris

Do not use Ilaris
- if you are allergic to canakinumab or any of the other ingredients of this medicine (listed in section 6).
- if you have, or suspect you have, an active, severe infection.

Warning and precautions
Talk to your doctor before using Ilaris if any of the following applies to you:
- if you currently have an infection or if you have had repeated infections or a condition such as a known low level of white blood cells which makes you more likely to get infections.
- if you have or have ever had tuberculosis or direct contact with a person with an active tuberculosis infection. Your doctor may also check whether you have tuberculosis using a specific test.
- if you have signs of an allergic reaction such as difficulty breathing or swallowing, nausea, dizziness, skin rash, itching, hives, palpitations or low blood pressure.
- if you have signs of a liver disorder such as yellow skin and eyes, nausea, loss of appetite, dark-coloured urine and light-coloured stools.
- if you need to have any vaccinations. You are advised to avoid being vaccinated with a type of vaccine called a live vaccine while being treated with Ilaris (see also "Other medicines (including vaccines) and Ilaris").

<u>Still's Disease</u>
- Patients with Still's disease may develop a condition called macrophage activation syndrome (MAS), which can be life-threatening. Your doctor will monitor you for potential triggering factors of MAS that include infections and re-activation of the underlying Still's disease (flare).

Children and adolescents
- CAPS and SJIA: Ilaris can be used in children aged 2 years and older.
- Gouty arthritis: Ilaris is not recommended for children or adolescents under 18 years of age.

Other medicines (including vaccines) and Ilaris
Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines.
- Live vaccines: you are advised to avoid being vaccinated with a type of vaccine called a live vaccine while being treated with Ilaris. Your doctor may want to check your vaccination history and give you any vaccinations that you have missed before you start treatment with Ilaris. If you need to be given a live vaccine after starting treatment with Ilaris, you are advised to wait for at least 3 months after the last Ilaris injection and before the next injection.
- Medicines called tumour necrosis factor (TNF) inhibitors, such as etanercept, adalimumab or infliximab. These are used mainly in rheumatic and autoimmune diseases. They should not be used with Ilaris because this may increase the risk of infections.

Pregnancy and breast-feeding
- Ilaris has not been studied in pregnant women. You are advised to avoid becoming pregnant and must use adequate contraception while using Ilaris and for at least 3 months after the last Ilaris treatment. It is important to tell your doctor if you are pregnant, if you think you may be pregnant or are planning to have a baby. Your doctor will discuss with you the potential risk of taking Ilaris during pregnancy.
- If you received canakinumab while you were pregnant, it is important that you inform the baby's doctor or nurse before any vaccinations are given to your baby. Your baby should not receive live vaccines until at least 16 weeks after you received your last dose of canakinumab before giving birth.
- It is not known whether Ilaris passes into human milk. Your doctor will discuss with you the potential risks of taking Ilaris before breast-feeding.

Driving and using machines
Ilaris treatment may give you a spinning sensation (dizziness/vertigo) or intense tiredness (asthenia). This may affect your ability to drive or use tools or machines. If you feel a spinning sensation or feel tired, do not drive or use any tools or machines until you are feeling normal again.

3. How to use Ilaris

If you have CAPS or Still's disease (AOSD or SJIA), you may inject yourself with Ilaris after proper training, or a caregiver may inject it for you.

Always use this medicine exactly as your doctor has told you. Check with your doctor, pharmacist or nurse if you are not sure.

If you have gouty arthritis, your treatment will be overseen by a doctor with specialist training. Ilaris should be injected by a healthcare professional only.

Keep your doctor informed of your condition and any symptoms before you use or are given Ilaris (see section 2). Your doctor may decide to delay or interrupt your treatment, but only if necessary.

Ilaris is intended for subcutaneous use. This means that it is injected through a short needle into the fatty tissue just under the skin.

How much Ilaris to use
Cryopyrin-Associated Periodic Syndromes
The recommended starting dose of Ilaris is:
Adults, adolescents and children aged 4 years or more
- 150 mg for patients with body weight more than 40 kg
- 2 mg/kg for patients with body weight of 15 kg or more, up to a maximum of 40 kg
- 4 mg/kg for patients with body weight of 7.5 kg or more, but below 15 kg

Children aged 2 or 3 years
- 4 mg/kg for patients with body weight of 7.5 kg or more

Ilaris is injected every 8 weeks as a single dose.

If you have not responded sufficiently to treatment after 7 days, your doctor may consider giving you a repeat dose of 150 mg or 2 mg/kg. If you respond sufficiently to this, your treatment will continue with this higher dose of 300 mg or 4 mg/kg every 8 weeks. If you do not respond sufficiently to the repeat dose, a third dose of Ilaris at 300 mg or 4 mg/kg can be considered, and if you respond sufficiently to that, your treatment may continue at 600 mg and 8 mg/kg every 8 weeks.

For patients given a starting dose of 4 mg/kg who have not responded sufficiently after 7 days, a second dose of 4 mg/kg can be considered. If the patient responds sufficiently to this, treatment may be continued with 8 mg/kg every 8 weeks.

Still's Disease (AOSD and SJIA)
The recommended dose of Ilaris for patients with Still's disease (AOSD or SJIA) with body weight of 7.5 kg and above is 4 mg/kg (up to a maximum of 300 mg). Ilaris is given as an injection under the skin every 4 weeks.

Gouty arthritis
Your doctor will discuss with you the need to start or adjust a urate lowering therapy to lower the uric acid level in your blood.

The recommended dose of Ilaris for adult gouty arthritis patients is 150 mg given as a single dose at the time of a gouty arthritis attack.

If you need another treatment with Ilaris, and got relief from the last dose, you must wait at least 12 weeks before the next dose.

Injecting Ilaris yourself or injecting a child with Ilaris
If you have CAPS or Still's disease (AOSD or SJIA), patients or caregivers of child patients may administer Ilaris injections themselves after proper training in the correct injection technique.
- The patient or caregiver and the doctor should decide together who will administer the Ilaris injections.
- The doctor or nurse will demonstrate how to administer Ilaris injections.
- Do not try to administer an injection yourself if you have not been properly trained or if you are not sure how to do it.
- Ilaris vials are for single use for individual use only. Only use the contents provided in the Ilaris injection kit.
- Never re-use the left-over solution or any parts of the kit.

For instructions on how to administer Ilaris injections, please read the section "Instructions for use" at the end of this leaflet. If you have any questions, talk to your doctor, pharmacist or nurse.

How long to use Ilaris
- If you have CAPS or Still's disease (AOSD or SJIA), you should continue using Ilaris for as long as the doctor tells you.

- If you have a gouty arthritis attack, you will be given a single dose of Ilaris. If you experience a new attack, your doctor may consider giving you a new dose of Ilaris but not earlier than 12 weeks from the previous dose.

If you use more Ilaris than you should
If you accidentally inject more Ilaris than the recommended dose, it is unlikely to be serious, but you should inform your doctor, pharmacist or nurse as soon as possible.

If you inject Ilaris sooner than you should
- In CAPS, you should not inject Ilaris earlier than 8 weeks after the last dose, unless your doctor tells you to.
- In Still's disease (AOSD or SJIA), you should not inject Ilaris earlier than 4 weeks after the last dose.

If you accidentally inject Ilaris sooner than you should, tell your doctor, pharmacist or nurse as soon as possible.

If you forget to use Ilaris
If you have CAPS or Still's disease (AOSD or SJIA) and have forgotten to inject a dose of Ilaris, inject the next dose as soon as you remember. Then talk to the doctor to discuss when you should inject the next dose. You should then continue with injections at the recommended intervals as before.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Most of the side effects are mild to moderate and will generally disappear a few days to a few weeks after treatment.

Some side effects could be serious. Tell your doctor immediately, if you notice any of the side effects below:
- Fever lasting longer than 3 days or any other symptoms that might be due to an infection. These include shivering, chills, malaise, loss of appetite, body aches, typically in connection with a sudden onset of illness, sore throat or mouth ulcers, cough, phlegm, chest pain, difficulty breathing, ear pain, prolonged headache or localised redness, warmth or swelling of your skin or inflammation of connective tissue (cellulitis). These symptoms could be due to an infection caused by low levels of white blood cells (called leucopenia or neutropenia). Your doctor may check your blood regularly if considered necessary.
- Allergic reactions with rash and itching and possibly also hives, difficulty breathing or swallowing, dizziness, unusual awareness of your heart beat (palpitations) or low blood pressure.

Other side effects of Ilaris include:
Very common (may affect more than 1 in 10 people):
- Sore throat, runny nose, blocked nose, sneezing, feeling of pressure or pain in the cheeks and/or forehead with or without fever (nasopharyngitis, pharyngitis, rhinitis, sinusitis).
- Combination of sore throat, fever, swollen or red tonsils, cough, difficulty to swallow and headache (tonsilitis), reported less frequently in gouty arthritis patients.
- Painful and frequent urination with or without fever (urinary tract infection).
- Drop in levels of blood platelets (called thrombocytopenia).
- Stomach pain and feeling sick (gastroenteritis).
- Abdominal pain.
- Pain in muscles, bones or joints.
- Abnormal kidney function test results (creatinine renal clearance decreased, proteinuria).
- Injection site reaction (such as redness, swelling, warmth and itching).

Common (may affect up to 1 in 10 people):
- Abnormal levels of triglycerides in your blood (lipid metabolism disorder).
- Abnormal liver function test results (transaminases increased).
- High level of bilirubin in the blood, with or without yellow skin and eyes (hyperbilirubinaemia).
- Feeling dizzy, spinning sensation (vertigo).
- Feeling weak or very tired (asthenia).
- Back pain.

Uncommon (may affect up to 1 in 100 people):
– Heartburn (gastro-oesophageal reflux).

Not known (frequency cannot be estimated from the available data):
– Being sick (vomiting).
– Increases in blood uric acid levels were observed in studies on gouty arthritis patients flaring.
– Prolonged fever (i.e. fever lasting longer than three days) or any other symptoms possibly related to an infection, such as prolonged cough, phlegm, chest pain, blood in sputum (saliva and phlegm that is coughed up), difficulty breathing, ear pain, prolonged headache or localised redness, warmth or swelling of your skin. These may be symptoms of a typical infection or one that may be more serious (opportunistic infections).

Tell your doctor or your child's doctor immediately if you notice any of these symptoms.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Ilaris

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the labels and carton. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C - 8°C).
Do not freeze.
Store in the original package in order to protect from light.

After reconstitution, from a microbiological point of view, the product should be used immediately. However, chemical and physical in-use stability has been demonstrated for 24 hours at 2°C - 8°C.

Do not use Ilaris if you notice that the solution is not clear to opalescent or contains particles.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Ilaris contains
– The active substance is canakinumab. One vial of powder contains 150 mg canakinumab. After reconstitution, each ml of solution contains 150 mg canakinumab.
– The other ingredients are:
Powder: sucrose, histidine, histidine hydrochloride monohydrate, polysorbate 80.
Solvent: water for injections.

What Ilaris looks like and contents of the pack
– Ilaris powder and solvent for solution for injection consists of a white powder (150 mg in a 6 ml glass vial) and a clear, colourless solvent (5 ml in a separate 6 ml glass vial).
– Ilaris powder and solvent for solution for injection is available in an injection kit containing 1 vial of powder for solution for injection, 1 vial of solvent, 1 injection syringe, 1 safety needle, 2 vial adapters and 4 cleansing swabs.

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Manufacturer
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This leaflet was last revised in

This medicine has been authorised under "exceptional circumstances". This means that because of the rarity of this disease it has been impossible to get complete information on this medicine. The European Medicines Agency will review any new information on this medicine every year and this leaflet will be updated as necessary.

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu

INSTRUCTIONS FOR USE OF ILARIS POWDER AND SOLVENT FOR SOLUTION FOR INJECTION (INJECTION KIT)

Read these instructions all the way through before starting to prepare your medicine.

- Your doctor or nurse will give you training on how to inject yourself (see Section 3: "Injecting Ilaris yourself or injecting a child with Ilaris").
- It takes about 30 minutes to prepare the injection.
- In this section, we call the injection kit the "kit".

Before you start:

1. Remove the kit from the refrigerator.
   - Check the expiry date on the outer carton.
   - Do not use after the expiry date which is stated on the labels and carton. The expiry date is the last day of the month indicated.

2. Let the kit stand unopened for 15 minutes.
   - This brings the contents to room temperature.
   - Do not try to heat the kit – let it warm up on its own.

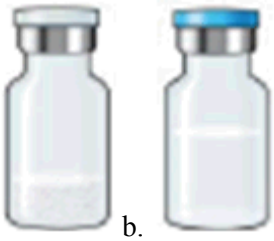
3. Find a clean place to prepare and give yourself the injection. Wash your hands with soap and water, then dry them on a clean towel.

4. Open the outer pack and take out all of the contents.
   - Check that you have all the items shown in the diagram below.
   - If any parts of the kit are missing or damaged, return the full pack to your doctor or pharmacist.
   - Only use the items which are in the kit – do not use anything else.

5. Do not touch the needles or the tops of the vials.

WHAT IS IN THE KIT:

a. b.



a. Powder vial
b. Solvent vial

c.



c. 1 ml injection syringe
d. Safety needle

d.



e. 2 vial adapters

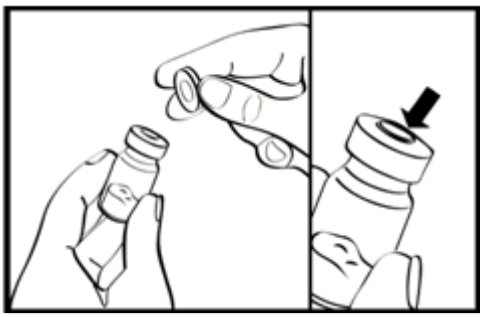
e.

f. 

f. 4 cleansing swabs

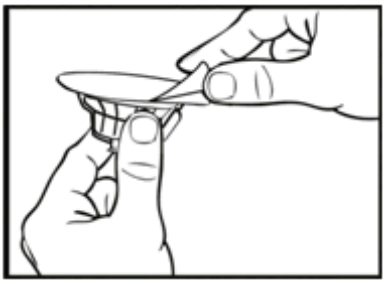
PREPARING THE MEDICINE

Step 1: Preparing the powder vial



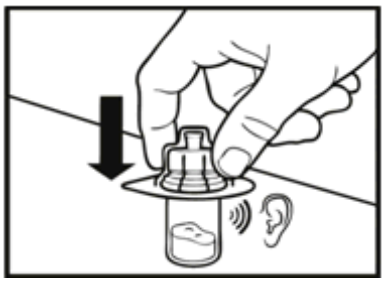
- Remove the flip-off cap from the powder vial.
- Use a fresh cleansing swab to wipe clean the rubber stopper.
- Do not touch the rubber stopper after it has been cleaned.

Step 2: Attaching the vial adapter to the powder vial



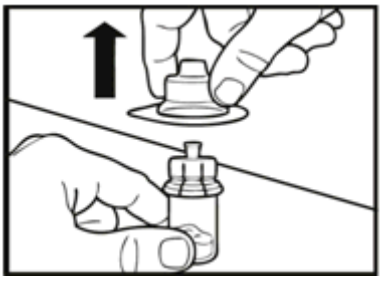
- Take one of the blister trays containing the vial adapters.
- Hold the blister tray firmly.
- Completely take off the film lid.
- Do not take the vial adapter out of the blister tray.

Do not touch the vial adapter at any stage.



Place the powder vial on a flat surface.

- Hold the blister tray and put the vial adapter on top of the powder vial.
- Push the blister tray down fully. You will hear the vial adapter snap into place.
  At this time the vial adapter is still inside the blister tray.



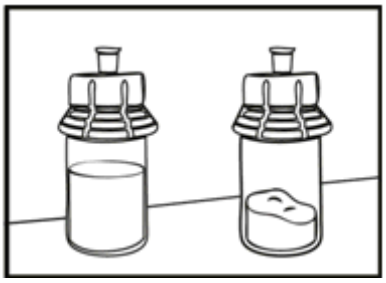
Hold the blister tray by the top.

- Lift the blister tray straight up so that it comes off the vial adapter.

Check that the vial adapter is in the correct position. If it is not:

- Do not touch the vial adapter.
- Put the blister tray back onto the vial adapter.
- Then change the position of the vial adapter.

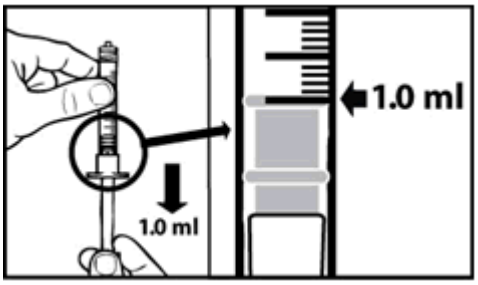
Step 3: Attaching the vial adaptor to the solvent vial



- Repeat steps 1 and 2 to put a vial adapter onto the solvent vial.
- The solvent vial contains water for injections.

The two vials now have their vial adapters connected. They are ready to be used.

Step 4: Drawing 1.0 ml of air into the syringe

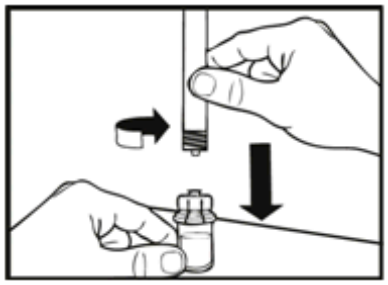


Peel off the film from the syringe pack and remove the syringe.

- Do not touch the tip of the syringe.
- Bring the syringe to eye level. This is so that you can measure the dose correctly.
- Pull the plunger downwards until the 1.0 ml mark is in line with the upper end of the plunger. This is shown in the diagram.

Drawing 1.0 ml of air into the syringe makes it easier to pull the water for injections into the syringe. It also helps to stop getting air bubbles in the syringe.

Step 5: Attaching the syringe to the solvent vial

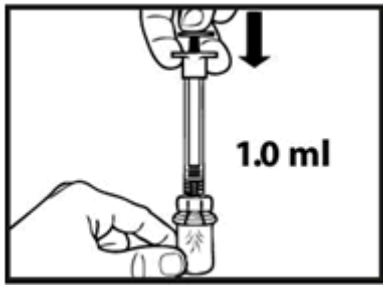


Do not touch the tips of the syringe or vial adapter while doing this.

- Hold the solvent vial.
- Gently screw the syringe onto the vial adapter.
- Do not use force.

A needle is not needed at this stage.

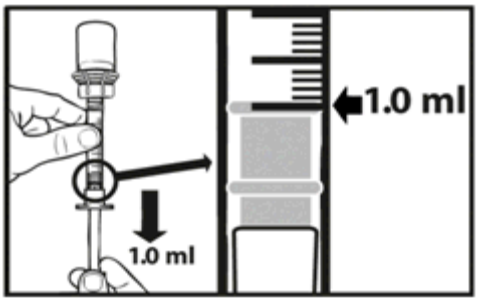
Step 6: Pushing 1.0 ml of air into the solvent vial



Slowly push the plunger all the way down.

- This will push the air that you have just drawn up into the syringe into the solvent vial.
- Keep the plunger held down.

Step 7: Drawing 1.0 ml of water into the syringe



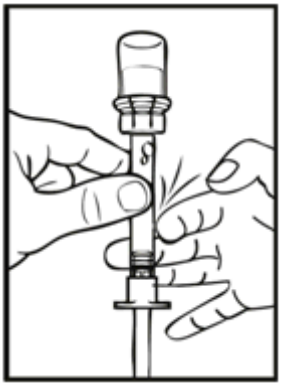
Turn the syringe to point upwards – this means that the solvent vial is now upside down.

- Bring the syringe to eye level. This is so that you can measure the dose correctly.
- Slowly pull the plunger downwards until the 1.0 ml mark on the syringe is in line with the upper end of the plunger. This is shown in the diagram.

Keep the vial upside down.

- Check the syringe for large air bubbles.

Step 8: Removing large air bubbles from the syringe



If there are any large air bubbles in the syringe, you need to remove them.

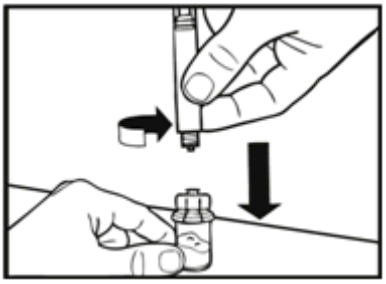
- Gently tap the syringe so the large air bubbles rise to the top.
- Carefully push the plunger up. This forces any large air bubbles into the vial.
- Then slowly pull the plunger back down to the 1.0 ml mark again.
- Repeat these steps until you have removed all the large bubbles.
- After this, check that the syringe still contains 1.0 ml of water.

Turn the syringe and vial round the other way. This means the vial is now at the bottom.

- Put the vial down on a clean and flat surface.
- Using a flat surface will help stop you from spilling the water.
- Hold the vial with one hand.
- With the other hand, hold the plunger and unscrew the syringe from the vial.

There will still be some water in the solvent vial.

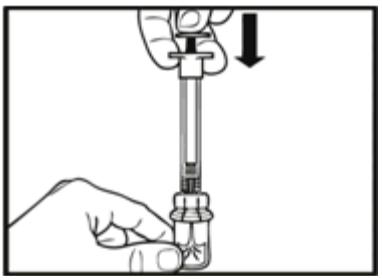
Step 9: Screwing the syringe onto the powder vial



Do not touch the tips of the syringe or the vial.

- Hold the powder vial on the clean and flat surface.
- Screw the syringe containing 1.0 ml of water onto the vial adapter.
- Do not force it.

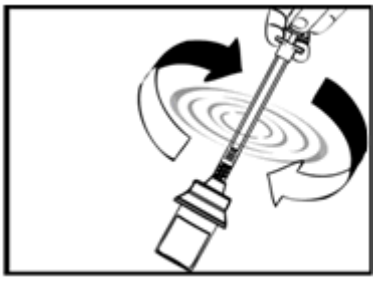
Step 10: Pushing 1.0 ml of water into the powder vial



Slowly push the plunger all the way in.

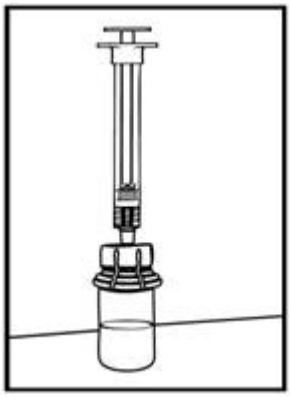
- This will push the water in the syringe into the powder vial.
- Do not take the syringe off yet.

Step 11: Mixing the powder and water



- Hold the syringe at an angle of about 45 degrees.
- Gently move the syringe and vial in a circle for at least 1 minute.
- Do it gently - do not shake the syringe and vial.

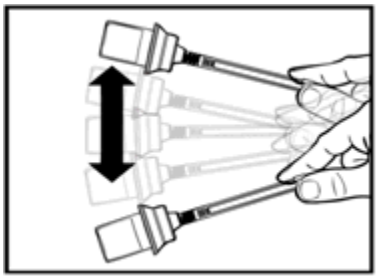
Step 12: Leaving the syringe and vial to stand



- Put the syringe and vial on a flat surface.
- Leave them to stand for 5 minutes.

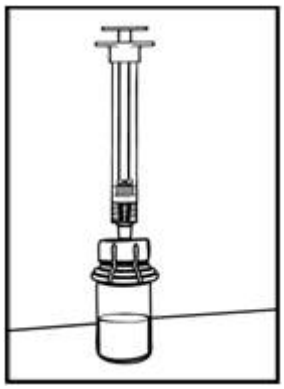
Do not worry if the plunger moves up. This can happen if there is slightly too much pressure in the vial.

Step 13: Mixing the powder and water again



- After 5 minutes, press the plunger all the way down, back into the syringe.
- Gently move the syringe and vial upwards until they are the other way up. Then turn the syringe and vial back again so they are back where they were.
- Do this ten times.
- Do it gently - do not shake the syringe and vial.

Step 14: Checking the medicine



- Leave the vial and syringe to stand for 15 minutes.

After 15 minutes, check that the medicine is not cloudy and does not have any bits in it.

- Do not shake the vial and syringe
- There may be foam on the top of the medicine. You do not need to worry about this.

If there are still bits in the medicine repeat Step 13.

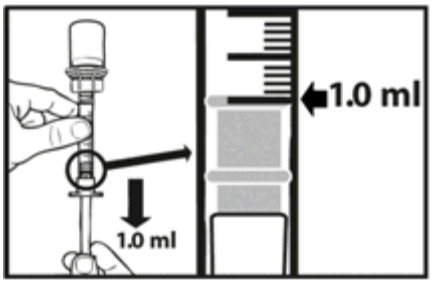
- Then, leave the vial and syringe to stand for another 5 minutes.
- Check the medicine again for any bits. If the medicine is not cloudy and does not have any bits in it, it is ready to use.

If you do not use your medicine straight away after you have prepared it:

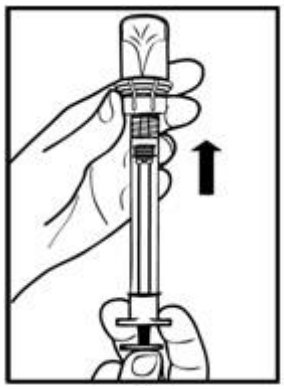
- Store the medicine in a refrigerator at a temperature of between 2°C and 8°C.
- Use your medicine within 24 hours.

GETTING READY TO INJECT THE PREPARED MEDICINE

Step 15: Filling the syringe with 1.0 ml of the prepared medicine



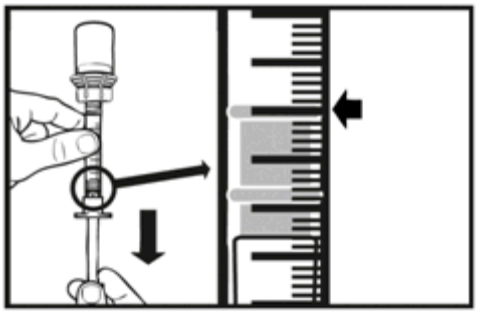
- Turn the syringe and vial upside down.
- Carefully pull the plunger down until the 1.0 ml mark is in line with the upper end of the plunger. This is shown in the diagram.
- Do not take the syringe off yet.



- Slowly push back the plunger all the way in. This will put all of the medicine back up into the vial.

Pushing back the plunger all the way in makes sure that the medicine is fully mixed. It also helps to stop air bubbles.

Step 16: Measuring the dose of your prepared medicine



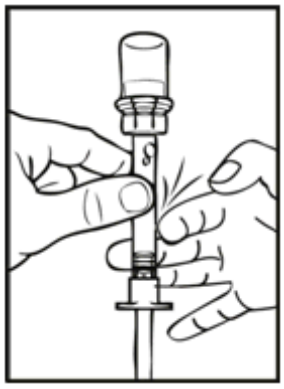
Your doctor will tell you what your dose of the medicine is.

- Bring the syringe to eye level. This is so that you can measure the dose correctly.
- The usual dose is between 0.2 and 1.0 ml.
- Slowly pull the plunger down again until the upper end of the plunger is in line with the mark for your dose of the medicine. This is shown in the diagram.

Keep the vial upside down.

- Check the medicine for large air bubbles.
- There may still be some medicine in the vial.

Step 17: Removing large air bubbles from the syringe



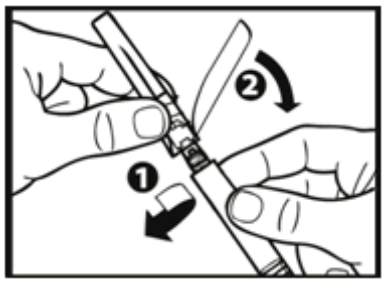
Remove any large air bubbles from the solution as follows:

- Gently tap the syringe so the large air bubbles rise to the top.
- Carefully push the plunger up. This will force any large air bubbles into the vial.
- Slowly pull the plunger back down to the dose prescribed by your doctor.
- Repeat these steps until all large bubbles have been removed.
- Check that the syringe contains the dose prescribed by your doctor.

Put the prepared syringe on a clean and flat surface.

- Using a flat surface will help stop you from spilling the medicine.
- Hold the plunger and unscrew the syringe.
- Do not touch the tip of the syringe.

Step 18: Attaching the needle

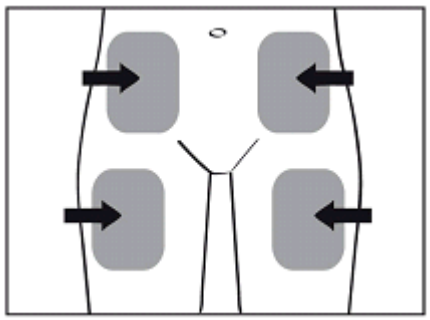


Do not touch the end of the needle or the tip of the syringe.

- Take the safety needle from its blister pack.
- Screw the safety needle onto the prepared syringe.
- Move the hinged safety guard back towards the syringe - as shown in the picture.

Place the syringe on a flat surface. Now choose the place on your body where you are going to give yourself the injection.

WHERE TO GIVE YOURSELF THE INJECTION



The shaded areas in this diagram show the places where you can give yourself the injection. Choose **one** of these places:

- your lower right stomach or
- your lower left stomach or
- your upper right thigh or
- your upper left thigh.

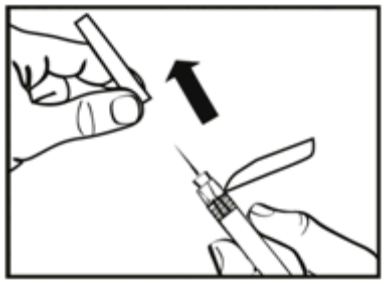
You can also give the injection into your upper arm or buttocks.

Choose a different place for each time you inject. This will help to stop soreness.

- Never inject in an area where your skin is sore or inflamed.

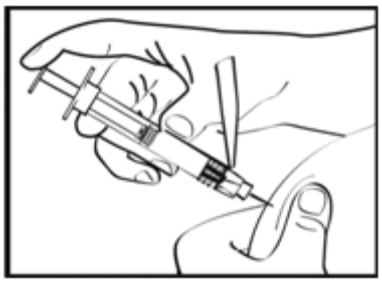
GIVING YOURSELF THE INJECTION

Step 19: Preparing your skin and the needle



- Clean the skin where you are going to give yourself the injection with a fresh cleansing swab.
- Pull the protective needle cap straight off the needle. Do not to touch or bend the needle.

Step 20: Giving yourself the injection



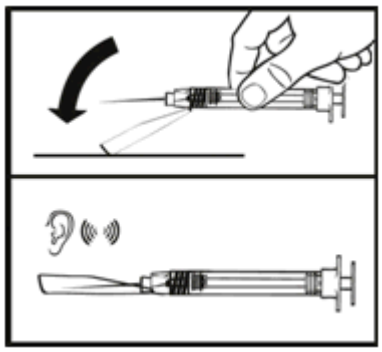
- Gently pinch up a fold of skin at the place you have chosen to give yourself the injection. This should be a fatty layer of skin.
- Hold the syringe as shown in the diagram.
- Put the whole needle straight into the skin fold at a right angle.
- Gently press in the plunger as far as it will go. This will inject the full dose.
- Then wait for 10 seconds and take the needle out of your skin.

If you start bleeding:

- Do not rub the injection area.
- Put a clean, dry cotton swab over the area.
- Press gently for 1 to 2 minutes. Then put on a plaster.

AFTER THE INJECTION

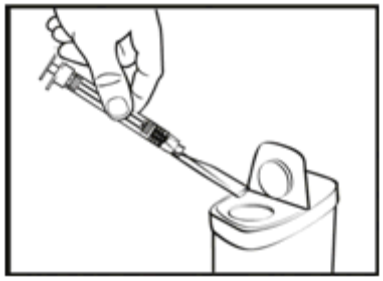
Step 21: Putting the safety guard on the needle



Put the safety guard on the needle straight away:

- Keep your fingers away from the needle tip and the safety guard.
- Press the needle safety guard down onto a hard surface such as a table. Do not use fingers to push the safety guard.
- You will hear a click when the safety guard has been put on the needle correctly.

Step 22: Disposal



Dispose of the syringe, the needle and the used vials, including any left-over solution, straight away.

- Put them in the sharps container or do as your doctor, nurse or pharmacist has told you if this is different.
- Keep the sharps container out of the reach of children.

Never try to re-use any parts of the kit or left-over solution.

1.7 同種同効品一覧表

本承認事項一部変更承認申請時点で，効能・効果，用法・用量，化学構造，薬理作用からみて本剤に類似していると考えられる同種同効品は存在しない。

1.8 添付文書（案）

最新の添付文書を参照する

日本標準商品分類番号	873999

貯法：
遮光し、凍結を避け、
2～8℃に保存

承認番号	22300AMX01216000
薬価収載	2011年11月
販売開始	2011年12月
国際誕生	2009年 6月
効能追加	2016年12月

ヒト型抗ヒトIL-1βモノクローナル抗体
生物由来製品、劇薬、処方箋医薬品
（注意－医師等の処方箋により使用すること）

イラリス®皮下注用150mg
ILARIS® for s.c. injection 150mg

カナキヌマブ（遺伝子組換え）凍結乾燥注射剤

使用期限：
包装に表示の使用期限内に
使用すること

NOVARTIS

【警告】

1. **本剤投与により、敗血症を含む重篤な感染症等があらわれることがあり、本剤との関連性は明らかではないが、悪性腫瘍の発現も報告されている。本剤が疾病を完治させる薬剤でないことも含め、これらの情報を患者に十分説明し、患者が理解したことを確認した上で、治療上の有益性が危険性を上回ると判断される場合にのみ本剤を投与すること。また、本剤の投与において、重篤な感染症等の副作用により、致命的な経過をたどることがあるので、緊急時に十分に措置できる医療施設及び医師のもとで投与し、本剤投与後に副作用が発現した場合には、速やかに担当医に連絡するよう患者に注意を与えること。**
2. **敗血症等の致命的な感染症が報告されているため、十分な観察を行うなど感染症の発現に注意すること。**
3. **＊＊本剤及びクリオピリン関連周期性症候群、家族性地中海熱、TNF受容体関連周期性症候群又は高IgD症候群（メバロン酸キナーゼ欠損症）について十分な知識をもつ医師が使用すること。**

【禁忌（次の患者には投与しないこと）】

1. 重篤な感染症の患者〔感染症が悪化するおそれがある。〕
2. 活動性結核の患者〔症状が悪化するおそれがある。〕
3. 本剤の成分に対し過敏症の既往歴のある患者

【組成・性状】

イラリス皮下注用150mgは、1バイアル中に下記成分・分量を含有する凍結乾燥注射剤で、日局注射用水1.0mLで用時溶解して用いる。

有効成分・含量（1バイアル中）	カナキヌマブ（遺伝子組換え）180.0mg[注1)] **本剤の調製方法に基づき、日局注射用水1.0mLで溶解したとき、液量1.2mL、濃度150mg/mLとなる。**
添加物（1バイアル中）	精製白糖 110.8mg L-ヒスチジン 3.361mg L-ヒスチジン塩酸塩水和物 2.008mg ポリソルベート80 0.720mg
性状	白色の塊又は粉末で、溶解後は無色～微黄褐色の澄明又は混濁した液
pH	6.2～6.8（溶解後）
浸透圧	390～490mOsm/kg（溶解後）

本剤の有効成分であるカナキヌマブ（遺伝子組換え）は、マウスハイブリドーマ細胞Sp2/0-Ag14から産生されるヒト型モノクローナル抗体である。マスターセルバンク及びワーキングセルバンク作製時の培地成分として、ヒト血清アルブミン（採血国：オランダ、採血方法：献血）及びヒト血清トランスフェリン（採血国：米国、採血方法：非献血）を使用している。

注1) 注射液吸引時の損失を考慮し、1バイアルから150mgを注射するに足る量を確保するために過量充填されている。

【効能又は効果】

1. **以下のクリオピリン関連周期性症候群**
   - **家族性寒冷自己炎症症候群**
   - **マックル・ウェルズ症候群**
   - **新生児期発症多臓器系炎症性疾患**
2. **＊＊既存治療で効果不十分な家族性地中海熱**
3. **＊＊TNF受容体関連周期性症候群**
4. **＊＊高IgD症候群（メバロン酸キナーゼ欠損症）**

＊＊<効能又は効果に関連する使用上の注意>
家族性地中海熱
コルヒチンによる適切な治療を行っても、疾患に起因する明らかな臨床症状が残る場合に投与すること。

【用法及び用量】

1. **クリオピリン関連周期性症候群**
   通常、体重40kg以下の患者にはカナキヌマブ（遺伝子組換え）として1回2mg/kgを、体重40kgを超える患者には1回150mgを8週毎に皮下投与する。
   十分な臨床的効果（皮疹及び炎症症状の寛解）がみられない場合には適宜漸増するが、1回最高用量は体重40kg以下の患者では8mg/kg、体重40kgを超える患者では600mgとする。
   最高用量まで増量し、8週以内に再燃がみられた場合には、投与間隔を4週間まで短縮できる。
   なお、症状に応じて1回投与量の増減を検討すること。
2. **＊＊家族性地中海熱及びTNF受容体関連周期性症候群**
   通常、体重40kg以下の患者にはカナキヌマブ（遺伝子組換え）として1回2mg/kgを、体重40kgを超える患者には1回150mgを、4週毎に皮下投与する。
   十分な臨床的効果がみられない場合には追加投与又は適宜漸増するが、1回最高用量は体重40kg以下の患者

では4mg/kg、体重40 kgを超える患者では300mgとする。

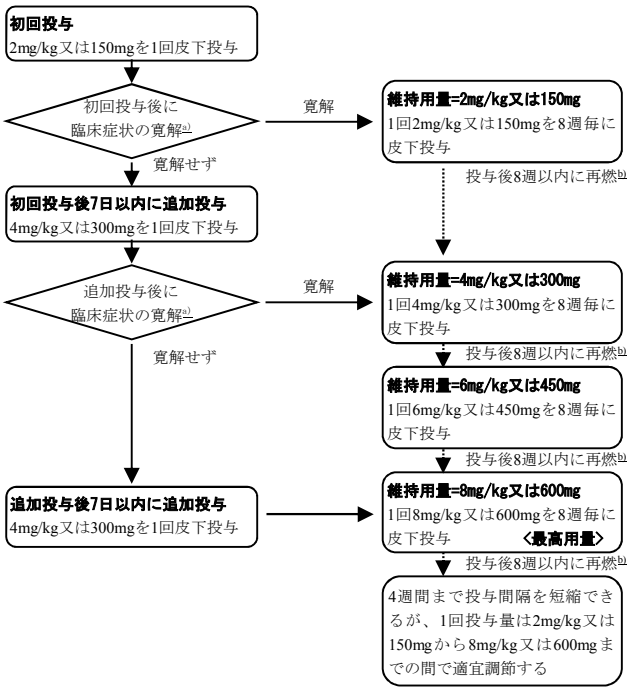
3. ****高IgD症候群（メバロン酸キナーゼ欠損症）**
通常、体重40kg以下の患者にはカナキヌマブ（遺伝子組換え）として1回2mg/kgを、体重40kgを超える患者には1回150mgを、4週毎に皮下投与する。
十分な臨床的効果がみられない場合には追加投与又は適宜漸増するが、1回最高用量は体重40kg以下の患者では6mg/kg、体重40kgを超える患者では450mgとする。

<用法及び用量に関連する使用上の注意>

1. 本剤1バイアルを日局注射用水1.0mLに溶解した場合、溶液1.0mLがカナキヌマブ（遺伝子組換え）の投与量150mgに相当する。（「8. 適用上の注意」の項参照）
2. **本剤の至適用量は患者の体重及び臨床症状によって異なり、投与量は患者毎に設定する必要がある。投与は1回2mg/kg又は150mgの低用量から開始し、十分な効果がみられない、もしくは再燃がみられた場合に限り、下表を参考に投与量の増量を行うこと。

十分な臨床的効果がみられない場合の漸増方法

クリオピリン関連周期性症候群の場合

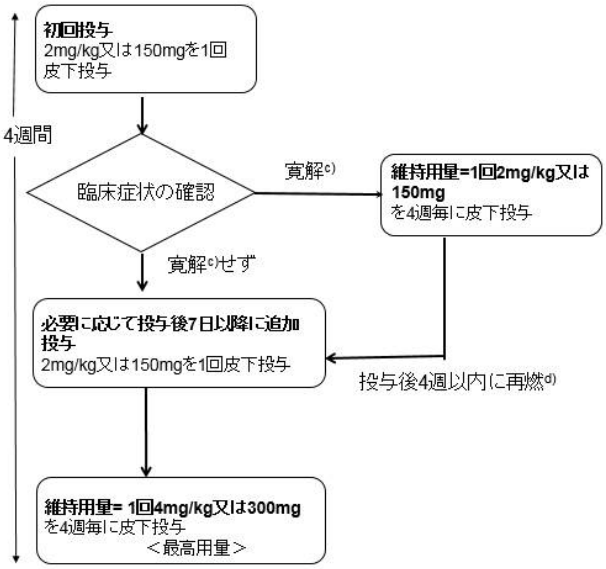


a)： 国内臨床試験における寛解の基準（以下の1～3をすべて満たす場合）
＜臨床的寛解＞
1．医師による自己炎症性疾患活動性の総合評価[注2)]が軽微以下
2．皮膚疾患の評価[注2)]が軽微以下
＜血清学的寛解＞
3．CRPが10mg/L（=1mg/dL）未満又はSAAが10mg/L（=10μg/mL）未満

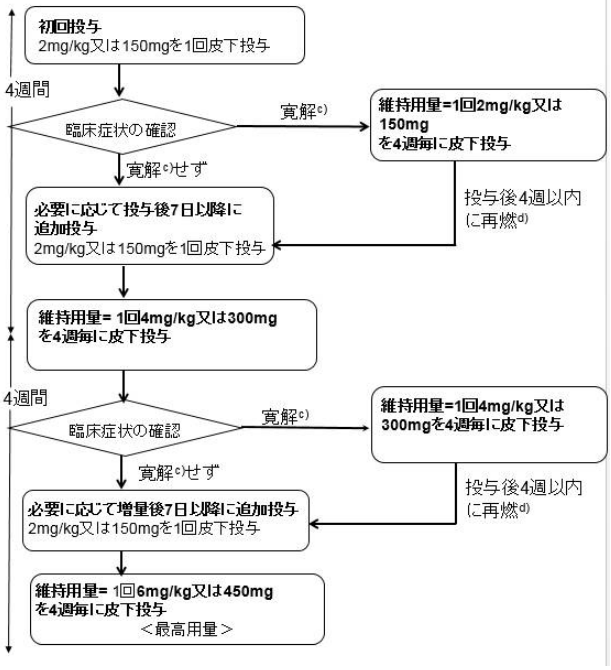
b)： 国内臨床試験における再燃の基準（以下の1～2をすべて満たす場合）
＜臨床的再燃＞
1．医師による自己炎症性疾患活動性の総合評価[注2)]が軽度以上、又は医師による自己炎症性疾患活動性の総合評価[注2)]が軽微かつ皮膚疾患の評価[注2)]が軽度以上
＜血清学的再燃＞
2．CRPが30mg/L（=3mg/dL）超又はSAAが30mg/L（=30μg/mL）超

注2）評価基準：なし、軽微、軽度、中等度、重度の5段階

****家族性地中海熱及びTNF受容体関連周期性症候群の場合**



****高IgD症候群（メバロン酸キナーゼ欠損症）の場合**



c) 臨床試験における寛解の基準
（以下の1～2をすべて満たす場合）
＜臨床的寛解＞
1.医師による自己炎症性疾患活動性の総合評価 [注3)] が軽微以下
＜血清学的寛解＞
2.CRPが10 mg/L以下又はベースラインと比べ70%以上の減少

d): 臨床試験における再燃の基準
（以下の1～2をすべて満たす場合）
＜臨床的再燃＞
1．医師による自己炎症性疾患活動性の総合評価[注3)]が軽度以上
＜血清学的再燃＞
2．CRPが30mg/L（=3mg/dL）以上

注3）評価基準：なし、軽微、軽度、中等度、重度の5段階

【使用上の注意】

１．慎重投与（次の患者には慎重に投与すること）

(1) 感染症の患者又は感染症が疑われる患者〔感染症が悪化するおそれがある。〕（「2. 重要な基本的注意」の項参照）

(2) 結核の既往歴を有する患者又は結核感染が疑われる患者〔結核を活動化させるおそれがある。〕（「2. 重要な基本的注意」の項参照）

(3) 再発性感染症の既往歴のある患者〔感染症が再発するおそれがある。〕（「2. 重要な基本的注意」の項参照）

(4) 易感染性の状態にある患者〔感染症を誘発するおそれがある。〕

２．重要な基本的注意

(1) **臨床試験において、上気道感染等の感染症が高頻度に報告されており、重篤な感染症も報告されているため、本剤投与中は感染症の発現、再発及び増悪に十分注意すること。（「4. 副作用⑴重大な副作用」の項参照）

(2) 本剤により感染に対する炎症反応が抑制される可能性があるため、本剤投与中は患者の状態を十分に観察すること。

(3) 本剤投与に先立って結核に関する十分な問診及び胸部X線（レントゲン）検査に加えインターフェロンγ遊離試験又はツベルクリン反応検査を行い、適宜胸部CT検査等を行うことにより、結核感染の有無を確認すること。結核の既往歴を有する場合及び結核感染が疑われる場合には、結核の診療経験がある医師に相談すること。以下のいずれかの患者には、原則として抗結核薬を投与した上で、本剤を投与すること。

1) 胸部画像検査で陳旧性結核に合致するか推定される陰影を有する患者
2) 結核の治療歴（肺外結核を含む）を有する患者
3) インターフェロンγ遊離試験やツベルクリン反応検査等の検査により、既感染が強く疑われる患者
4) 結核患者との濃厚接触歴を有する患者

また、本剤投与中も、胸部X線検査等の適切な検査を定期的に行うなど結核症の発現には十分に注意し、患者に対し、結核を疑う症状（持続する咳、体重減少、発熱等）が発現した場合には速やかに担当医に連絡するよう説明すること。なお、結核の活動性が確認された場合は結核の治療を優先し、本剤を投与しないこと。

(4) 本剤投与により好中球減少があらわれることがあるので、初回投与前、概ね投与1ヵ月後、及びその後本剤投与中は定期的に好中球数を測定すること。（「4. 副作用⑴重大な副作用」の項参照）

(5) **臨床試験において、アナフィラキシー又はアナフィラキシーショックは報告されていないが、本剤の投与に対する過敏症反応が報告されているため、重篤な過敏症反応のリスクを除外することはできない。本剤を投与する際には過敏症反応の発現に注意し、必要に応じて適切な処置を行うこと。

(6) 本剤を投与された患者において、悪性腫瘍が報告されている。本剤を含む抗IL-1製剤との関連性は明らかではないが、悪性腫瘍等の発現には注意すること。

(7) 本剤投与中は、生ワクチン接種による感染症発現のリスクを否定できないため、生ワクチン接種は行わないこと。本剤投与前に、必要なワクチンを接種しておくことが望ましい。

(8) 本剤は、マスターセルバンク及びワーキングセルバンク作製時において、培地成分の一部としてヒト血清アルブミン及びヒト血清トランスフェリンを使用しているが、最終製品の成分としては含まれていない。これらヒト血液由来成分のうち、ヒト血清アルブミンの原血漿に対してC型肝炎ウイルス（HCV）に対する核酸増幅検査を実施している。原血漿を対象としたその他の核酸増幅検査は実施していないが、血清学的検査によりウイルスの抗原又はウイルスに対する抗体が陰性であることを確認している。更に、これらヒト血液由来成分及びカナキヌマブ（遺伝子組換え）の製造において、複数の工程によりウイルスの除去・不活化をしており、最終製品へのB型肝炎ウイルス（HBV）、C型肝炎ウイルス（HCV）及びヒト免疫不全ウイルス（HIV-1及びHIV-2）混入の可能性は極めて低い。また、ヒト血清アルブミンの製造にオランダで採血したヒト血液を用いているが、本剤の投与により伝達性海綿状脳症（TSE）がヒトに伝播したとの報告はなく、TSEに関する理論的なリスク評価値は、一定の安全性を確保する目安に達しており、本剤によるTSE伝播のリスクは極めて低い。本剤の投与に際しては、その旨の患者又はその保護者への説明を考慮すること。

３．相互作用

本剤と他の薬剤との相互作用を検討した臨床試験は実施されていない。

代謝酵素チトクロームP450（CYP450）の発現は、IL-1β等の炎症性サイトカインにより抑制されているとの報告があり、本剤のIL-1β阻害作用により、CYP450の発現が増加する可能性がある。CYP450により代謝され、治療域が狭い薬剤と併用する場合には、これらの薬剤の効果や血中濃度に関するモニタリングを行い、必要に応じて投与量を調節すること。

併用注意（併用に注意すること）

薬剤名等	臨床症状・措置方法	機序・危険因子
抗 TNF 製剤	重篤な感染症発現のリスクが増大するおそれがある。また、他の抗 IL-1 製剤と抗 TNF 製剤との併用により、重篤な感染症の発現頻度増加が認められているため、本剤との併用は行わないことが望ましい。	共に免疫抑制作用を有するため。

４．**副作用

クリオピリン関連周期性症候群患者の国内臨床試験（D2308試験）において、19例中12例（63.2%）に副作用が認められた。主な副作用は鼻咽頭炎3例（15.8%）、口内炎2例（10.5%）等であった。

クリオピリン関連周期性症候群患者の海外臨床試験（A2102試験、D2304試験、D2306試験の併合解析）において、169例中68例（40.2%）に副作用が認められ

た。主な副作用は頭痛7例（4.1%）、体重増加7例（4.1%）、回転性めまい6例（3.6%）、気管支炎5例（3.0%）等であった。（承認時までの集計）
家族性地中海熱患者、TNF受容体関連周期性症候群患者、高IgD症候群（メバロン酸キナーゼ欠損症）患者の国際共同試験（N2301試験）において、169例(日本人8例を含む)中47例（27.8%）に副作用が認められた。主な副作用は注射部位反応13例（7.7%）、頭痛5例（3.0%）等であった。（承認時までの集計）

「重大な副作用」及び「その他の副作用」について、クリオピリン関連周期性症候群患者の国内臨床試験及び家族性地中海熱患者、TNF受容体関連周期性症候群患者、高IgD症候群（メバロン酸キナーゼ欠損症）患者の国際共同試験における日本人患者で認められなかった副作用は頻度不明とした。

(1) 重大な副作用

1) ****重篤な感染症**（6.7%）：敗血症や日和見感染症（アスペルギルス症、非定型抗酸菌症、帯状疱疹等）等の重篤な感染症があらわれることがあるので、本剤投与後は患者の状態を十分に観察し、異常が認められた場合には感染症に対する治療を行い、本剤の投与は継続しないこと。
2) **好中球減少**（頻度不明）：好中球減少があらわれることがあるので、定期的に血液検査を実施するなど観察を十分に行い、異常が認められた場合には投与を中止するなど、適切な処置を行うこと。

(2) ****その他の副作用

	頻度不明	5%以上	5%未満
感染症	尿路感染、気管支炎、ウイルス感染、扁桃炎、鼻炎、耳感染、咽頭炎、外陰部膣カンジダ症、下気道感染、肺感染	鼻咽頭炎	胃腸炎、肺炎、副鼻腔炎、上気道感染
神経系	回転性めまい	－	頭痛
過敏症	過敏症反応	－	－
皮膚	－	－	注射部位反応
消化器	下痢	口内炎	－
肝臓	AST（GOT）・ALT（GPT）上昇	－	－
その他	体重増加、血小板数減少	－	－

５．高齢者への投与

一般に高齢者では生理機能が低下しているので注意すること。

６．妊婦、産婦、授乳婦等への投与

(1) 妊婦又は妊娠している可能性のある婦人には、治療上の有益性が危険性を上回ると判断される場合にのみ投与すること。〔妊娠中の投与に関する安全性は確立していない。動物実験（マーモセット）で胎児への移行が認められている。〕
(2) 授乳婦に投与する場合には、授乳を中止させること。〔動物実験（マウス）でマウス抗マウスIL-1β抗体を母動物に授乳期まで投与した際、マウス新生児に同抗体が移行したとの報告がある。〕

７．小児等への投与

低出生体重児、新生児、乳児又は2歳未満の幼児に対する、安全性及び有効性は確立していない（使用経験がない）。

８．適用上の注意

(1) **投与経路**
本剤の投与は皮下投与のみとすること。
(2) **調製前の準備**
巻末の投与液量一覧表を参考に、必要数のバイアル、日局注射用水注入用注射筒（1mL）、投与用注射筒（必要液量を正確に採取できる注射筒）及び注射針（21ゲージ及び27ゲージ）を用意すること。
(3) **調製方法**
1）本剤は泡立ちやすいので、調製する際は、バイアルを振らない等、注意すること。
2）本剤の溶解には日局注射用水以外は使用しないこと。
3）バイアルのゴム栓部分をアルコール綿等で消毒する。
4）**21ゲージ**の注射針を装着した1mLの注射筒を用いて、本剤1バイアルに日局注射用水**1.0mL**をゆっくりと注入して溶解する（**液量は1.2mLとなる**）。
5）約45°の角度でバイアルを約1分間ゆっくりと回転させた後、5分間静置する。
6）バイアルをゆっくりと10回上下反転させる。可能であれば、指でゴム栓に触れないようにする。このときバイアルを振らないこと。
7）室温で約15分間静置する。
8）バイアルの側面を軽く叩き、ゴム栓に付着している液体を下に移動させる。この溶液には肉眼で確認できる粒子はほとんど含まれておらず、澄明又は混濁している。
9）溶解後60分以内に使用しない場合は、冷蔵庫内（2～8℃）で保管し、24時間以内に使用すること。使用後の残液は使用しないこと。
(4) **投与時**
1）溶液内に粒子がある場合等、外観に異常を認めた場合には使用しないこと。
2）**本剤1バイアルを日局注射用水1.0mLに溶解した場合、溶液1.0mLがカナキヌマブ（遺伝子組換え）の投与量150mgに相当する**。投与量に応じて必要な液量を、**21ゲージ**の注射針を装着した注射筒を用いて注

意深く採取する。このとき、必要液量を正確に採取できる注射筒を用いること。
3) 採取後、**27ゲージ**の注射針を用いて皮下投与する。
4) 瘢痕組織への投与を避けること。
5) 1回につき1.0mLを超えて投与する場合には、1箇所あたり1.0mLを超えないように部位を分けて投与すること。

９．その他の注意

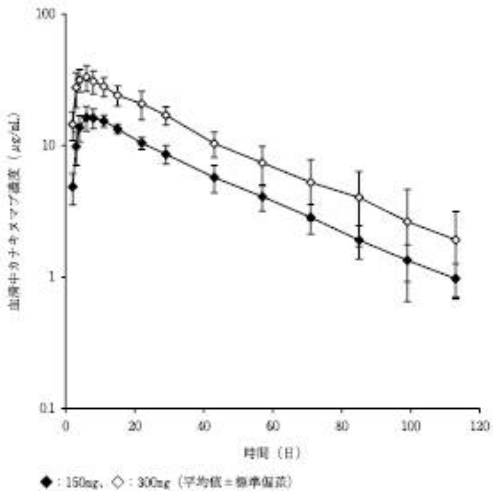
(1) **クリオピリン関連周期性症候群患者を対象とした国内及び海外臨床試験において、白血球数及び血小板数の平均値が減少したが、これらの変動は炎症反応の低下による可能性がある。

(2) **クリオピリン関連周期性症候群患者を対象とした海外臨床試験において、トランスアミナーゼ上昇を伴わない、無症候性で軽度の血清ビリルビン上昇が報告されている。

【薬物動態】

１．**健康成人での成績

日本人健康成人男子にカナキヌマブ（遺伝子組換え）150mg又は300mgを皮下投与したとき、血清中カナキヌマブ濃度は投与後5日目に最高となり、消失半減期は約26日であった。[1)]



◆：150mg、◇：300mg（平均値＋標準偏差）

日本人健康成人男子にカナキヌマブ（遺伝子組換え）150mg又は300mgを単回皮下投与したときの血清中濃度推移（n=6）

日本人健康成人男子にカナキヌマブ（遺伝子組換え）150mg又は300mgを単回皮下投与したときの薬物動態パラメータ（n=6）

	150mg	300mg
Cmax（μg/mL）	16.9±2.62	34.1±6.09
Tmax（day）	5［5～10］	5［2～5］
$AUC_{0\text{-}inf}$（μg・day/mL）	663±79.6	1,300±275
$T_{1/2}$（day）	26.3±2.02	26.9±8.23
CL/F（L/day）	0.229±0.0319	0.238±0.0421
Vz/F（L）	8.70±1.34	8.92±1.64

平均値±標準偏差、Tmaxに関しては中央値［最小～最大］

日本人健康成人男子にカナキヌマブ（遺伝子組換え）を静脈内投与したときのクリアランス（CL）は0.160～0.174L/day、定常状態における分布容積（Vss）は5.44～5.77Lであった。カナキヌマブ（遺伝子組換え）150mg～300mgの皮下投与時又は0.30～10.0mg/kgの静脈内投与時、AUC及びCmaxは用量に比例して増加した。[1)]（本剤の承認された用法及び用量は【用法及び用量】の項参照）

２．**患者での成績

（１）**クリオピリン関連周期性症候群患者

母集団薬物動態-薬力学解析よりベイズ推定したD2308試験の日本人クリオピリン関連周期性症候群患者（平均体重：28.8kg）のCL及びVssの平均値±標準偏差は0.0925±0.049L/day及び2.48±1.20Lであった。

外国人成人クリオピリン関連周期性症候群患者にカナキヌマブ（遺伝子組換え）150mgを皮下投与したとき、血清中カナキヌマブ濃度は投与後約7日目に最高となり、消失半減期は約26日であった。また、皮下投与時のバイオアベイラビリティは約67%であった。4～17歳の外国人クリオピリン関連周期性症候群患者にカナキヌマブ（遺伝子組換え）2mg/kg又は150mgを皮下投与したとき、血清中カナキヌマブ濃度は投与後2～7日目に最高となり、薬物動態パラメータの値は18歳以上の外国人で認められている値と同程度であった。[2)]

母集団薬物動態-薬力学解析の結果、カナキヌマブ（遺伝子組換え）のクリアランス及び分布容積は体重に依存することが示された。

（２）**クリオピリン関連周期性症候群患者、家族性地中海熱患者、TNF受容体関連周期性症候群患者、高IgD症候群（メバロン酸キナーゼ欠損症）患者

日本人及び外国人のクリオピリン関連周期性症候群患者、家族性地中海熱患者、TNF受容体関連周期性症候群患者、高IgD症候群（メバロン酸キナーゼ欠損症）患者から得られた血清中カナキヌマブ濃度を用いて母集団薬物動態解析を実施した。カナキヌマブ（遺伝子組換え）のクリアランス及び分布容積は体重に依存することが示された。平均体重（55kg）でのCL及びVssの母集団平均値はそれぞれ0.14L/day及び4.96Lであった。日本人と外国人でカナキヌマブ（遺伝子組換え）の薬物動態は同様であった。[3)]

【臨床成績】

１．クリオピリン関連周期性症候群（家族性寒冷自己炎症症候群、マックル・ウェルズ 症候群、新生児期発症多臓器系炎症性疾患）

（1）．国内臨床試験（D2308試験）

クリオピリン関連周期性症候群（マックル・ウェルズ症候群又は新生児期発症多臓器系炎症性疾患）患者19例（2～14歳の患者11例を含む）を対象に体重40kg以下の患者には本剤1回2mg/kg、体重40kgを超える患者には本剤1回150mgを皮下投与し、寛解[a)]が得られない場合又は投与後8週以内に再燃[b)]がみられた場合は本剤1回2mg/kg又は150mgずつ増量して投与した。ただし、1回最高用量は本剤8mg/kg又は600mgとした。その結果、投与24週以内及び投与48週以内に寛解した患者の割合はそれぞれ94.7%（18/19例）及び100%（19/19例）、寛解した患者のうち投与24週後及び投

与48週後の時点で再燃がみられなかった患者の割合はそれぞれ77.8%（14/18例）及び84.2%（16/19例）であった。また、初回投与後14日以内に炎症マーカーであるCRP及び血清アミロイドA蛋白（SAA）の低下がみられた。[4)]

a)、b)：〈用法及び用量に関連する使用上の注意〉「十分な臨床的効果がみられない場合の漸増方法」の脚注参照

（２）．海外臨床試験

1) クリオピリン関連周期性症候群（A2102試験）

NALP3（NLRP3）変異を有するクリオピリン関連周期性症候群患者34例（4～17歳の患者7例を含む）を対象に、初回投与時及び再燃時に16歳未満の患者（5例）には本剤1回2mg/kg、16歳以上の患者には本剤1回150mgを皮下投与した。その結果、16歳未満の患者では初回投与後2～8日以内に5例全例、16歳以上の患者では初回投与後2～9日以内に96.6%（28/29例）の患者が寛解した。また、初回投与後1週間以内にCRP及びSAAの低下がみられた。[2)]

2) クリオピリン関連周期性症候群（D2306試験）

本剤による治療未経験のクリオピリン関連周期性症候群患者109例（3～17歳の患者38例を含む）、A2102及びD2304試験からの移行例57例（5～17歳の患者9例を含む）、計166例を対象に実施した。治療未経験例には初回用量として体重40kg以下の患者には本剤1回2mg/kg、体重40kgを超える患者には本剤1回150mgを8週毎に皮下投与し、再燃がみられた場合には1回最高用量として本剤8mg/kg又は600mgまで漸増し、6ヵ月～最長2年間投与した。その結果、試験全体では投与終了時までに再燃が一度もみられなかった患者の割合は76.5%（127/166例）であった。また、治療未経験例では78.0%（85/109例）の患者が初回投与後21日以内に寛解した。[5)]

3) マックル・ウェルズ症候群（D2304試験）

マックル・ウェルズ症候群患者35例を対象とし、全例に初回用量として体重15～40kgの患者には本剤1回2mg/kg、体重40kgを超える患者には本剤1回150mgを皮下投与した。この初回投与で寛解した患者に対して、8週後以降は体重15～40kgの患者には本剤1回2mg/kg又はプラセボ、体重40kgを超える患者には本剤1回150mg又はプラセボを8週毎に再燃がみられるまで投与し（二重盲検期：最大24週間）、再燃後又は24週経過後は全例に体重15～40kgの患者には本剤1回2mg/kg、体重40kgを超える患者には本剤1回150mgを8週毎に投与した。その結果、初回投与後8週以内に97.1%（34/35例）の患者が寛解した。二重盲検期の24週以内に本剤投与群全例（15例）で再燃がみられなかったのに対し、プラセボ投与群では81.3%（13/16例）で再燃がみられた。24週後以降も投与を継続した31例中、再燃がみられたのは1例であった。また、初回投与後8日以内にCRP及びSAAの低下がみられた。[6)]

２．**家族性地中海熱、TNF受容体関連周期性症候群、高IgD症候群（メバロン酸キナーゼ欠損症）

国際共同試験（N2301試験）

コルヒチン効果不十分又は不耐容な家族性地中海熱患者（crFMF）63例(日本人1例を含む)、TNF受容体関連周期性症候群患者（TRAPS）46例(日本人6例を含む)、高IgD症候群患者（HIDS）／メバロン酸キナーゼ欠損症患者（MKD）72例(日本人1例を含む)を対象に、体重40kg以下の患者には本剤1回2mg/kg又はプラセボ、体重40kgを超える患者には本剤1回 150mg又はプラセボを4週毎に再燃がみられるまで投与し（二重盲検期：最大16週間）、寛解（〈用法及び用量に関連する使用上の注意〉「十分な臨床的効果がみられない場合の漸増方法」の脚注参照)が得られない場合は本剤1回2mg/kg又は150mgずつ増量して投与した。ただし、1回最高用量は本剤4mg/kg又は300mgとした。16週後に寛解が得られた患者の割合（投与14日後にindex flareの寛解[a)]が得られ、かつ16週間の投与中に新たな再燃[b)]が認められなかった患者の割合）を次表に示す。本剤投与群における16週後に寛解が得られた患者の割合は、いずれの疾患群でもプラセボ群に比べて有意に高かった。また、いずれの疾患群でも初回投与後14日以内に炎症マーカーであるCRP及び血清アミロイドA蛋白（SAA）の低下がみられた。[7)]

疾患	本剤群	プラセボ群	プラセボ群との差［95%CI］#、p値##
TRAPS	45 (10/22)	8 (2/24)	37 [8, 61] p=0.0050
HIDS/MKD	35 (13/37)	6 (2/35)	29 [6, 50] p=0.0020
crFMF	61 (19/31)	6 (2/32)	55 [31, 73] p<0.0001

%(例数)

正確な信頼区間

Fisher’s exact検定

a) Index flareの寛解：ランダム化時に認められた最初の再燃をindex flareとし、投与１４日後に以下の2つの条件を満たした場合、index flareの寛解とした。

・ 臨床的寛解：医師による全般評価が軽微以下

・ 血清学的寛解：CRPが正常範囲内（10 mg/L以下）又はベースラインと比べ70%以上の減少

b) 新たな再燃：臨床的再燃と血清学的再燃が同時に認められた場合と定義した。

・ 臨床的再燃：医師による全般評価が軽度以上

・ 血清学的再燃：CRP 30 mg/L以上

【薬効薬理】

カナキヌマブ（遺伝子組換え）は、ヒトIL-1βに対する遺伝子組換えヒトIgG1モノクローナル抗体である。ヒトIL-1βに結合し、IL-1βが受容体に結合することを阻害することにより、その活性を中和する。

１．IL-1β阻害作用

カナキヌマブ（遺伝子組換え）は、ヒトIL-1βに結合（解離定数：約40pM）し、ヒトIL-1βとヒトIL-1受容体との結合を阻害した。[8,9)]

２．*In vitro*における薬理活性

カナキヌマブ（遺伝子組換え）は、ヒトIL-1βによるヒト皮膚線維芽細胞からのIL-6産生及びヒト黒色腫細胞におけるIL-8のプロモーター活性を抑制した。[10,11)]

３．*In vivo*における薬理活性

カナキヌマブ（遺伝子組換え）は、ヒトIL-1β誘発マウス関節炎の腫脹を単回腹腔内投与で抑制した。[12)] また、ヒトIL-1βで誘発されるマウス空気嚢への好中球浸潤を単回腹腔内投与で抑制した。[13)] 更に、ヒト

IL-1βにより誘発されるラットの発熱を単回静脈内投与で抑制した。[14)]

4．その他の作用

カナキヌマブ（遺伝子組換え）は、in vitroでヒト混合リンパ球反応におけるT細胞増殖を阻害しなかった。[15)]

【有効成分に関する理化学的知見】

一般名：カナキヌマブ（遺伝子組換え）
Canakinumab（Genetical Recombination）

分子量：約148,000

本　質：ヒトIL-1βに対する遺伝子組換えヒトIgG1モノクローナル抗体であり、マウスハイブリドーマ細胞Sp2/0-Ag14により産生される448個のアミノ酸残基からなる重鎖（$C_{2196}H_{3387}N_{587}O_{669}S_{16}$；分子量：49,227.96）2分子及び214個のアミノ酸残基からなる軽鎖（$C_{1030}H_{1596}N_{274}O_{336}S_5$；分子量：23,353.65）2分子で構成される糖蛋白質

****【承認条件】**

医薬品リスク管理計画を策定の上、適切に実施すること。

クリオピリン関連周期性症候群

国内での治験症例が極めて限られていることから、再審査期間又は一定数の症例に係るデータが蓄積されるまでの間は、本剤投与症例全例を登録して安全性及び有効性に関する製造販売後調査を実施すること。その中で、感染症等の発現を含めた長期投与時の安全性及び有効性について十分に検討すること。

TNF受容体関連周期性症候群、高IgD症候群（メバロン酸キナーゼ欠損症）、既存治療で効果不十分な家族性地中海熱

国内での治験症例が極めて限られていることから、再審査期間又は一定数の症例に係るデータが蓄積されるまでの間は、本剤投与症例全例を登録して安全性及び有効性に関する製造販売後調査を実施すること。その中で、感染症等の発現を含めた長期投与時の安全性及び有効性について十分に検討すること。

【包装】

イラリス皮下注用150mg　1バイアル

【主要文献】

1) 社内資料：日本人健康成人男子を対象とした単回投与試験（A1101）〔ILAU00001〕
2) 社内資料：外国人クリオピリン関連周期性症候群患者を対象とした第Ⅰ/Ⅱa相試験（A2102）〔ILAU00002〕
3) **社内資料：母集団薬物動態解析　〔20160943〕
4) Imagawa,T.et al.：Clin.Exp.Rheumatol.31（2）,302,2013〔ILAM00316〕
5) Kuemmerle-Deschner,J.B.et al.：Ann.Rheum.Dis.70（12）,2095,2011〔ILAF00001〕
6) Lachmann,H.J.et al.：New Engl.J.Med.360（23）,2416,2009〔ILAM00009〕
7) **社内資料：周期性発熱症候群患者を対象とした国際共同試験（N2301、二重盲検期）〔20160944〕
8) 社内資料：ヒトIL-1βに対する結合親和性〔ILAU00003〕
9) 社内資料：ヒトIL-1βの受容体との結合に対する阻害作用〔ILAU00004〕
10) 社内資料：ヒトIL-1βによるヒト皮膚線維芽細胞からのIL-6産生に対する抑制作用〔ILAU00005〕
11) 社内資料：ヒトIL-1βによるヒト黒色腫細胞のIL-8プロモーター活性に対する抑制作用〔ILAU00006〕
12) 社内資料：ヒトIL-1βによるマウス膝関節の腫脹に対する抑制作用〔ILAU00007〕
13) 社内資料：ヒトIL-1βによるマウス空気嚢への好中球浸潤に対する抑制作用〔ILAU00008〕
14) 社内資料：ヒトIL-1βによるラット発熱に対する抑制作用〔ILAU00009〕
15) 社内資料：ヒト混合リンパ球反応に対する作用〔ILAU00010〕

【文献請求先】

主要文献に記載の社内資料につきましても下記にご請求下さい。

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＜参考＞

イラリス®皮下注用150mg投与液量一覧表

体重40kg以下の患者に対する投与液量=用量レベル×患者の体重÷投与濃度

用量レベル=1 回 2 mg/kg （体重40kg以下の患者）
1 回150mg （体重40kgを超える患者）

体重	カナキヌマブ（遺伝子組換え）1 回投与用量	投与液量	投与濃度※
8 kg	16mg	0.11mL	150mg/mL
10kg	20mg	0.13mL	
12kg	24mg	0.16mL	
14kg	28mg	0.19mL	
16kg	32mg	0.21mL	
18kg	36mg	0.24mL	
20kg	40mg	0.27mL	
22kg	44mg	0.29mL	
24kg	48mg	0.32mL	
26kg	52mg	0.35mL	
28kg	56mg	0.37mL	
30kg	60mg	0.40mL	
32kg	64mg	0.43mL	
34kg	68mg	0.45mL	
36kg	72mg	0.48mL	
38kg	76mg	0.51mL	
40kg	80mg	0.53mL	
>40kg	150mg	1.0mL	

用量レベル= 1 回 6mg/kg （体重40kg以下の患者）
1 回450mg （体重40kgを超える患者）

体重	カナキヌマブ（遺伝子組換え）1 回投与用量	投与液量	投与濃度※
8 kg	48mg	0.32mL	150mg/mL
10kg	60mg	0.40mL	
12kg	72mg	0.48mL	
14kg	84mg	0.56mL	
16kg	96mg	0.64mL	
18kg	108mg	0.72mL	
20kg	120mg	0.80mL	
22kg	132mg	0.88mL	
24kg	144mg	0.96mL	
26kg	156mg	1.04mL	
28kg	168mg	1.12mL	
30kg	180mg	1.20mL	
32kg	192mg	1.28mL	
34kg	204mg	1.36mL	
36kg	216mg	1.44mL	
38kg	228mg	1.52mL	
40kg	240mg	1.60mL	
>40kg	450mg	3.0mL	

用量レベル=1 回 4mg/kg （体重40kg以下の患者）
1 回300mg （体重40kgを超える患者）

体重	カナキヌマブ（遺伝子組換え）1 回投与用量	投与液量	投与濃度※
8 kg	32mg	0.21mL	150mg/mL
10kg	40mg	0.27mL	
12kg	48mg	0.32mL	
14kg	56mg	0.37mL	
16kg	64mg	0.43mL	
18kg	72mg	0.48mL	
20kg	80mg	0.53mL	
22kg	88mg	0.59mL	
24kg	96mg	0.64mL	
26kg	104mg	0.69mL	
28kg	112mg	0.75mL	
30kg	120mg	0.80mL	
32kg	128mg	0.85mL	
34kg	136mg	0.91mL	
36kg	144mg	0.96mL	
38kg	152mg	1.01mL	
40kg	160mg	1.07mL	
>40kg	300mg	2.0mL	

用量レベル= 1 回 8mg/kg （体重40kg以下の患者）
1 回600mg （体重40kgを超える患者）

体重	カナキヌマブ（遺伝子組換え）1 回投与用量	投与液量	投与濃度※
8 kg	64mg	0.43mL	150mg/mL
10kg	80mg	0.53mL	
12kg	96mg	0.64mL	
14kg	112mg	0.75mL	
16kg	128mg	0.85mL	
18kg	144mg	0.96mL	
20kg	160mg	1.07mL	
22kg	176mg	1.17mL	
24kg	192mg	1.28mL	
26kg	208mg	1.39mL	
28kg	224mg	1.49mL	
30kg	240mg	1.60mL	
32kg	256mg	1.71mL	
34kg	272mg	1.81mL	
36kg	288mg	1.92mL	
38kg	304mg	2.03mL	
40kg	320mg	2.13mL	
>40kg	600mg	4.0mL	

※ 本剤は、注射液吸引時の損失を考慮し、1バイアルから150mgを注射するに足る量を確保するために過量充填されている。本剤1バイアルを日局注射用水1.0mLで溶解したとき、液量1.2mL、濃度150mg/mLとなる。

1.8.2 効能・効果（案），用法・用量（案）及び その設定根拠

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略号一覧

略号	略していない表現 (英)	略していない表現 (日)
ACZ885	canakinumab	カナキヌマブ
CAPS	Cryopyrin-Associated Periodic Syndrome	クリオピリン関連周期性症候群
crFMF	colchicine resistant Familial Mediterranean Fever	コルヒチン抵抗性家族性地中海熱
CRP	c-reactive protein	C 反応性蛋白
HIDS	Hyper IgD Syndrome	高 IgD 症候群
IG	immunoglobulin	免疫グロブリン
IL	interleukin	インターロイキン
MKD	Mevalonate Kinase Deficiency	メバロン酸キナーゼ欠損症
SAA	serum amyloid A	血清アミロイド A
TNF	Tumor Necrosis Factor	腫瘍壊死因子
TRAPS	TNF Receptor-Associated Periodic Syndrome	TNF 受容体関連周期性症候群

用語の定義一覧

用語	定義
Index flare	ランダム化時に認められた最初の再燃であり，本試験の有効性評価の指標となる再燃
Index flare の寛解	以下の 2 つの条件を満たした場合，index flare の寛解とした。 • 臨床的寛解：医師による全般評価が軽微以下 • 血清学的寛解：CRP が正常範囲内（10 mg/L 以下）又はベースラインと比べ 70%以上の減少
再燃	再燃は，臨床的再燃と血清学的再燃が同時に認められた場合と定義した。 • 臨床的再燃：医師による全般評価が軽度以上 • 血清学的再燃：CRP 30 mg/L 以上 Day 15 に index flare の寛解が得られた被験者は，Day 15 以降にこの定義を適応した。

1 効能・効果及びその設定根拠

1.1 効能・効果

1. クリオピリン関連周期性症候群：家族性寒冷自己炎症症候群，マックル・ウェルズ症候群，新生児期発症多臓器系炎症性疾患
2. 家族性地中海熱
3. TNF 受容体関連周期性症候群
4. メバロン酸キナーゼ欠損症／高 IgD 症候群

1.2 効能・効果の設定根拠

本項では，既承認のクリオピリン関連周期性症候群（Cryopyrin-Associated Periodic Syndromes，以下 CAPS）に加え，上記下線部を追加効能・効果として承認事項一部変更承認申請するための根拠を記載する。

家族性地中海熱（Familial Mediterranean Fever，以下 FMF），TNF 受容体関連周期性症候群（TNF Receptor-Associated Periodic Syndrome，以下 TRAPS）又はメバロン酸キナーゼ欠損症（Mevalonate Kinase Deficiency，以下 MKD）／高 IgD 症候群（Hyper IgD Syndrome，以下 HIDS）は CAPS と同じく周期性発熱症候群に属し，いずれも日常生活に支障を来すほどの高熱を伴う全身性炎症発作を繰り返し，炎症性サイトカインの標的となる器官・組織に特有の徴候及び症状（漿膜炎，好中球性皮疹，粘膜潰瘍，関節痛・関節炎，無菌性髄膜炎・頭痛）を伴う。原因遺伝子はそれぞれ異なるものの，それらの遺伝子変異は間接的にインフラマソームを活性化し，IL-1β の分泌を促進すると推察されている。IL-1β は炎症誘発物質であり，ヒト及びラットにおいて炎症及び発熱反応を惹起する（Elkordy et al. 1997，Dascombe et al. 1989）。

カナキヌマブは，ヒト IL-1β に対する遺伝子組換えヒト IgG1 モノクローナル抗体であり，IL-1βに結合しIL-1βのIL-1β受容体への結合を阻害することにより，その生物活性を中和するため，CAPS と同様に FMF，TRAPS，MKD/HIDS における IL-1β の過剰産生による慢性的な炎症反応や進行性の組織障害を抑制することが期待できると考え，これらの疾患に対する開発を計画した。

MKD は，メバロン酸キナーゼ遺伝子の変異によって，メバロン酸キナーゼ活性が欠乏することで引き起こされる（van der Hilst et al. 2005）。本疾患は，血清 IgD が高値を示す患者が多いことから，当初，HIDS と命名された。しかし，IgD の上昇を認めないことも多く（難病情報センター 2012b），近年は本疾患の本態はメバロン酸キナーゼ活性の低下であると考えられている。しかし，HIDS の方が疾患名として長期間用いられており，臨床現場ではいずれの疾患名も使用されているため，本承認事項一部変更承認申請での追加効能・効果はメバロン酸キナーゼ欠損症と高 IgD 血症を併記することとした。後述する N2301 試験計画当時には，HIDS が用いられていたため，対象疾患名を HIDS として実施した（以下，N2301 試験の対象患者を示す場合は，HIDS と記載）。

カナキヌマブの有効性及び安全性は，コルヒチン抵抗性あるいは不耐容の FMF（以下 crFMF），TRAPS 及び HIDS の患者を対象に，日本人患者も含む国際共同治験として実施した N2301 試験で評価した[2.7.6-N2301 試験]。

N2301 試験での結果，有効性の主要評価項目である Week 16 の寛解率は，crFMF，TRAPS，HIDS いずれの疾患においても，プラセボ群に対する 2 mg/kg（40 kg を超える場合は 150 mg） 4 週間隔投与群の優越性が示された。Week 16 の寛解率（2 mg/kg 4 週間隔投与群，プラセボ群）は crFMF（61.29%，6.25%），TRAPS（45.45%，8.33%），HIDS（35.14%，5.71%）であり，寛解率の投与群間差（2 mg/kg 4 週間隔投与群 − プラセボ群）は crFMF，TRAPS 及び HIDS でそれぞれ 55%，37%，29%であった。カナキヌマブの効果はいずれの疾患においても速やかに認められ，Day 15 の早期から医師による全般評価，CRP，血清アミロイド A の減少がみられ，Week 16 時までその減少が維持された。カナキヌマブは crFMF，TRAPS，HIDS に対し，症状の再燃をコントロールし，全身性の炎症を改善することが確認された。日本人部分集団でも，全体集団と同様にカナキヌマブ投与により症状の改善が認められた。[2.5-4 項]

N2301 試験における死亡の報告はなかった。重篤な有害事象，治験薬の投与中止に至った有害事象，休薬又は減量を要した有害事象の発現はわずかであった。報告された有害事象は，カナキヌマブの既承認の適応症に対する使用経験から，これまでに有害事象として報告されているものであり，crFMF，TRAPS，HIDS で新たに認められたものはなかった。有害事象の主な内容は，crFMF，TRAPS，HIDS とも共通して鼻咽頭炎及び上気道感染等の感染症，下痢及び腹痛等の胃腸障害，発熱，注射部位反応，頭痛であった。重症度は軽度又は中等度の事象が多かった。ほとんどが処置なし，薬物治療等の処置により消失し，治験薬の投与中止や休薬を要することなく管理可能であった。カナキヌマブの既承認の適応症での使用経験から予測された，感染症，好中球減少症が crFMF，TRAPS，HIDS でも認められたが，重症度及び発現率ともに CAPS で認められたものから大きく異なることはなく，新たなリスクは特定されなかった。N2301 試験の結果，既存治療によっても十分な効果が得られない crFMF，TRAPS，HIDS に対し，カナキヌマブを投与した場合の安全性プロファイルは，既承認の適応症から特定された安全性プロファイルと同様であった[2.5-5 項]。

以上より，カナキヌマブの FMF，TRAPS，MKD/HIDS に対する有効性は N2301 試験の 16 週の寛解率を主要評価項目として，プラセボ群に対する 2 mg/kg 4 週間隔投与群の優越性がいずれの疾患でも示され，また安全性プロファイルは既承認の適応症から特定されているものと同様であり，新たなリスクは特定されなかったため，周期性発熱性症候群の FMF，TRAPS，MKD/HIDS を効能・効果として追加することとした。

本承認事項一部変更承認申請で追加する効能・効果の 3 疾患のうち，唯一 FMF ではコルヒチンの有効性が確立している。N2301 試験では FMF の治療として推奨されているコルヒチンに対して抵抗性又は不耐容を示した患者を対象として実施し，上述の有効性及び安全性を評価した。し

かし，2016 年 9 月時点で，本邦ではコルヒチンは FMF に対して適応を取得していないため，本承認事項一変承認申請での追加効能・効果は「家族性地中海熱」とし，既存治療に対する抵抗性及び不耐容を示している患者を対象としたことは使用上の注意として記載した。

なお，FMF に対する治療薬としてコルヒチンが平成 28 年 9 月 28 日に承認された。コルヒチンの承認及び審査中の独立行政法人医薬品医療機器総合機構との協議内容を踏まえ，効能又は効果（案）を以下の通り変更した。

【効能又は効果（案）】（下線部が本一変申請追加箇所）

1. 以下のクリオピリン関連周期性症候群
   - 家族性寒冷自己炎症症候群
   - マックル・ウェルズ症候群
   - 新生児期発症多臓器系炎症性疾患
2. 既存治療で効果不十分な家族性地中海熱
3. TNF 受容体関連周期性症候群
4. 高 IgD 症候群（メバロン酸キナーゼ欠損症）

1.3 効能・効果に関連する使用上の注意

家族性地中海熱の場合
既存治療で効果不十分又は忍容性のない患者に投与すること。

1.4 効能・効果に関連する使用上の注意の設定根拠

本承認事項一変承認申請で追加する効能・効果の 3 疾患のうち，TRAPS 及び MKD/HIDS に対して国内外で承認されている薬剤はなく，確立された治療法はない。FMF の治療は，厚生労働省難治事業研究班報告（厚生労働省 2015c）によると，FMF の診断が確定した場合コルヒチンを投与すべきであると記載されており，ほとんどの日本人 FMF 患者に，薬事承認上は適応外ではあるがコルヒチンが投与されていると考えられる。

上述の背景を踏まえ，本承認事項一変承認申請で追加する効能・効果の患者を対象として実施し，日本人患者も参加した国際共同治験である N2301 試験では，TRAPS，MKD/HIDS に対し，既存治療に関する選択基準は設定しなかった。一方，FMF では，診断確定後，ほとんどの場合まずコルヒチンが投与されることから，コルヒチン投与によっても疾患活動性が認められる又は不耐容の患者を対象とした。そのため，前項で述べた N2301 試験の結果は crFMF 患者を対象として得られたものであり，コルヒチン抵抗性あるいは不耐容の患者以外では，カナキヌマブの有効性及び安全性は確認されていないため，使用上の注意として記載することとした。なお，本邦にお

いて 2016 年 9 月時点においてはコルヒチンは FMF の適応を有していないため，「既存治療」と言及した。

なお，FMF への有効性が確立されているコルヒチンが平成 28 年 9 月 28 日に承認されたこと及び，審査中の独立行政法人医薬品医療機器総合機構との協議内容を踏まえ，効能又は効果に関連する使用上の注意（案）を以下の通り変更した。

＜効能又は効果に関連する使用上の注意（案）＞
家族性地中海熱
コルヒチンによる適切な治療を行っても，疾患に起因する明らかな臨床症状が残る場合に投与すること。

2 用法及び用量及びその設定根拠

2.1 用法及び用量

1. クリオピリン関連周期性症候群
   通常，体重 40 kg 以下の患者にはカナキヌマブ（遺伝子組換え）として 1 回 2 mg/kg を，体重 40 kg を超える患者には 1 回 150 mg を 8 週毎に皮下投与する。
   十分な臨床的効果（皮疹及び炎症症状の寛解）がみられない場合には適宜漸増するが，1 回最高用量は体重 40 kg 以下の患者では 8 mg/kg，体重 40 kg を超える患者では 600 mg とする。
   最高用量まで増量し，8 週以内に再燃がみられた場合には，投与間隔を 4 週間まで短縮できる。
   なお，症状に応じて 1 回投与量の増減を検討すること。
2. 家族性地中海熱及び TNF 受容体関連周期性症候群
   通常，体重 40 kg 以下の患者にはカナキヌマブ（遺伝子組換え）として 1 回 2 mg/kg を，体重 40 kg を超える患者には 1 回 150 mg を，4 週毎に皮下投与する。
   十分な臨床効果がみられない場合には，投与後 7 日以降に，体重 40 kg 以下の患者には 1 回 2 mg/kg を，体重 40 kg を超える患者には 1 回 150 mg を，必要に応じて追加投与する。
   また，4 週毎の次回投与時より，1 回投与量をそれぞれ 4 mg/kg，300 mg に原則として増量する。
   なお，症状に応じて 1 回投与量の増減を検討するが，1 回最高用量は体重 40 kg 以下の患者では 4 mg/kg，体重 40 kg を超える患者では 300 mg を超えないこと。

3. メバロン酸キナーゼ欠損症／高 IgD 症候群
通常，体重 40 kg 以下の患者にはカナキヌマブ（遺伝子組換え）として 1 回 2 mg/kg を，体重 40 kg を超える患者には 1 回 150 mg を，4 週毎に皮下投与する。
十分な臨床効果がみられない場合には，投与後 7 日以降に，体重 40 kg 以下の患者には 1 回 2 mg/kg を，体重 40 kg を超える患者には 1 回 150 mg を，必要に応じて追加投与する。また，4 週毎の次回投与時より，1 回投与量をそれぞれ 4 mg/kg，300 mg に原則として増量する。
増量後十分な臨床効果がみられない場合には，増量後 7 日以降に，体重 40 kg 以下の患者には 1 回 2 mg/kg を，体重 40 kg を超える患者には 1 回 150 mg を必要に応じて追加投与する。また，4 週毎の次回投与時より，1 回投与量をそれぞれ 6 mg/kg，450 mg に原則として増量する。
なお，症状に応じて 1 回投与量の増減を検討するが，1 回最高用量は体重 40 kg 以下の患者では 6 mg/kg，体重 40 kg を超える患者では 450 mg を超えないこと。

2.2 用法及び用量の設定根拠

本項では，効能・効果追加に伴い，上記下線部を用法及び用量として承認事項一部変更承認申請するための根拠を記載する。

FMF，TRAPS 及び MKD/HIDS における用法及び用量は日本人患者も参加した N2301 試験で用いた用法及び用量を基に設定した。また，MKD/HIDS の用法及び用量は，カナキヌマブを投与した MKD/HIDS 対象の臨床研究の結果も参考とした。

N2301 試験ではいずれの疾患に対しても，2 mg/kg（40 kg を超える場合は 150 mg）を初回用量として，4 週間隔で投与し，効果不十分な場合には 4 mg/kg（40 kg を超える場合は 300 mg）に増量する用法用量でカナキヌマブを投与した。

FMF 及び TRAPS における用法用量は，N2301 試験で有効性が検証され，安全性が確認された。

2 mg/kg（40 kg を超える場合は 150 mg） 4 週間隔投与で，Week 16 での寛解率（2 mg/kg 4 週間隔投与群，プラセボ群）は crFMF で（61.29%，6.25%），TRAPS で（45.45%，8.33%）であり，寛解率の投与群間差（2 mg/kg 4 週間隔投与群 − プラセボ群）は crFMF で 55%，TRAPS で 37%であり，プラセボ群に対する 2 mg/kg 4 週間隔投与群の優越性が示された。

寛解率に対する N2301 試験の主要評価項目の主解析と 4 mg/kg（40 kg を超える場合は 300 mg）への増量効果を評価するために実施した寛解率に対する探索的解析[2.5-4.6 項]を，Day 8~28 に 2 mg/kg の追加投与又は 4 mg/kg に増量した場合の影響を評価するため比較した。その結果，2 mg/kg 4 週間隔投与群で，寛解率は主解析の結果では crFMF で 61.29%（19/31 名），TRAPS で 45.45%（10/22 名）であった。一方，探索的解析の結果では，寛解率は crFMF で 70.97%（22/31 名），TRAPS で 72.73%（16/22 名）であり，主解析と比べてさらに crFMF で約 10%，TRAPS で

約 27%の被験者が寛解したことから，増量の効果が示された。さらに，CRP，血清アミロイド A は治験薬投与開始後にベースラインと比べて減少し，Week 17 では正常範囲内，正常値をわずかに上回る程度までの改善が見られた被験者がいた一方で，正常値より高い被験者もいた。これらの結果から，2 mg/kg では再燃のコントロールが得られない患者が存在し，これらの患者に対して 4 mg/kg に増量することで再燃をコントロールできることを示すと考える。

日本人患者でも，全体集団と同様に，カナキヌマブ投与による臨床的なベネフィットが得られ，安全性は日本人患者集団と全体集団で同様であった。

MKD/HIDS における用法用量も，N2301 試験で有効性が検証され，安全性が確認された。

HIDS において，2 mg/kg（40 kg を超える場合は 150 mg） 4 週間隔投与で Week 16 での寛解率（2 mg/kg 4 週間隔投与群，プラセボ群）は（35.14%，5.71%）で，寛解率の投与群間差（2 mg/kg 4 週間隔投与群 − プラセボ群）は 29%であり，プラセボ群に対する 2 mg/kg 4 週間隔投与群の優越性が示された。

寛解率に対する N2301 試験の主要評価項目の主解析と 4 mg/kg（40 kg を超える場合は 300 mg）への増量効果を評価するために実施した寛解率に対する探索的解析[2.5-4.6 項]を，Day 8~28 に 2 mg/kg の追加投与又は 4 mg/kg に増量した場合の影響を評価するため比較した。その結果，2 mg/kg 4 週間隔投与群で，寛解率は主解析の結果では 35.14%（13/37 名）であった。一方，探索的解析の結果では，寛解率は 56.76%（21/37 名）であり，主解析と比べてさらに約 22%の被験者が寛解したことから，増量の効果が示された。

しかしながら，2 mg/kg から投与を開始し 4 mg/kg へ増量した被験者では，CRP，血清アミロイド A が十分に改善しない被験者が存在した。CRP，血清アミロイド A ともに治験薬投与開始後ベースラインと比べて減少したものの Week 17 では CRP は正常値をわずかに上回る程度まで改善したが，血清アミロイド A は正常値より高く，特に血清アミロイド A では，crFMF，TRAPS と比べても程度が高かった。このことから，MKD/HIDS では 4 mg/kg に増量しても十分に再燃のコントロールが得られない患者が存在すると考えた。[2.5-4.6 項]

N2301 試験中では，6 mg/kg（40 kg を超える場合は 450 mg）での有効性及び安全性については確認されていない。しかし，国内で HIDS 患者に対する臨床研究が[redacted]で実施中で，1 名の重症型の HIDS 患者が参加しており，本承認申請時点で 6 mg/kg の 4 週間隔投与が継続中である。体重 40 kg 以下の HIDS 患者に対する 6 mg/kg の 4 週間隔投与の用法用量は N2301 試験で検討されていないが，国内で承認されている CAPS での用法用量の範囲内である。本臨床研究の研究医が作成した中間報告書によると，4 mg/kg から 6 mg/kg への増量によって嘔吐等の発作回数が減少したことにより，6 mg/kg がより有効であることが示唆されたが，継続投与を妨げるような安全性の問題は報告されていない。

以上より，MKD/HIDS の用法用量については，本臨床研究で使用されている 6 mg/kg（40 kg を超える場合は 450 mg）まで増量可能となるよう設定した。

さらに，N2301 試験の投与中断・投与頻度低減期の結果から，TRAPS，HIDS，crFMF に対する用法について考察する。

Week 40 の寛解率は，いずれの疾患でもプラセボ群に比べ 150 mg q8w 群で高く，150 mg q8w 投与で一定の効果が認められた。しかしながら，カナキヌマブ 150 mg の 8 週間隔投与でのプラセボに対する優越性は示されなかった。また，TRAPS，crFMF では約半数，HIDS では大半が疾患活動性をコントロールするために 150 mg q8w より高い用法用量を要した。150 mg q8w 投与又は 300 mg q8w 投与の被験者のいずれでも再燃が認められており，特に HIDS で再燃のリスクが高く，十分に再燃のコントロールが得られない患者が多く存在した。[2.5-4.6 項]このことから，TRAPS，HIDS，crFMF 患者に対し，疾患活動性をより適切にコントロールするには，本剤の用法を 4 週間隔とすることがより望ましいと考えた。

なお，審査中の独立行政法人医薬品医療機器総合機構との協議内容を踏まえ，用法及び用量（案）を以下の通り変更した。

【用法及び用量（案）】

1. クリオピリン関連周期性症候群

   通常、体重 40 kg 以下の患者にはカナキヌマブ（遺伝子組換え）として 1 回 2 mg/kg を、体重 40 kg を超える患者には 1 回 150 mg を 8 週毎に皮下投与する。

   十分な臨床的効果（皮疹及び炎症症状の寛解）がみられない場合には適宜漸増するが、1 回最高用量は体重 40 kg 以下の患者では 8 mg/kg、体重 40 kg を超える患者では 600 mg とする。

   最高用量まで増量し、8 週以内に再燃がみられた場合には、投与間隔を 4 週間まで短縮できる。

   なお、症状に応じて 1 回投与量の増減を検討すること。

2. 家族性地中海熱及び TNF 受容体関連周期性症候群

   通常、体重 40 kg 以下の患者にはカナキヌマブ（遺伝子組換え）として 1 回 2 mg/kg を、体重 40 kg を超える患者には 1 回 150 mg を、4 週毎に皮下投与する。

   十分な臨床的効果がみられない場合には追加投与又は適宜漸増するが、1 回最高用量は体重 40 kg 以下の患者では 4 mg/kg、体重 40kg を超える患者では 300 mg とする。

3. 高 IgD 症候群（メバロン酸キナーゼ欠損症）

   通常、体重 40 kg 以下の患者にはカナキヌマブ（遺伝子組換え）として 1 回 2 mg/kg を、体重 40 kg を超える患者には 1 回 150 mg を、4 週毎に皮下投与する。

   十分な臨床的効果がみられない場合には追加投与又は適宜漸増するが、1 回最高用量は体重 40 kg 以下の患者では 6 mg/kg、体重 40 kg を超える患者では 450 mg とする。

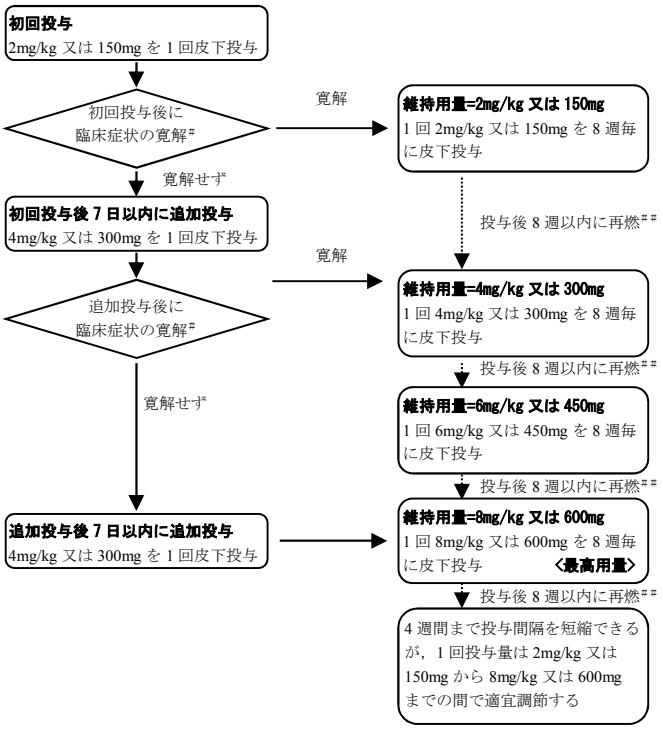
2.3 用法及び用量に関連する使用上の注意

（1）本剤 1 バイアルを日局注射用水 1.0 mL に溶解した場合，溶液 1.0 mL がカナキヌマブ（遺伝子組換え）の投与量 150 mg に相当する。（「8．適用上の注意」の項参照）

（2）本剤の至適用量は患者の体重及び臨床症状によって異なり，投与量は患者ごとに設定する必要がある。投与は 1 回 2 mg/kg 又は 150 mg の低用量から開始し，十分な効果がみられない，若しくは再燃がみられた場合に限り，投与量の増量を行うこと。

十分な臨床的効果がみられない場合の漸増方法

クリオピリン関連周期性症候群の場合



＃： 国内臨床試験における寛解の基準（以下の 1～3 をすべて満たす場合）

臨床的寛解

1. 医師による自己炎症性疾患活動性の総合評価[注 2)] が軽微以下
2. 皮膚疾患の評価[注 2)] が軽微以下

血清学的寛解

3. CRP が 10 mg/L（=1 mg/dL）未満又は SAA が 10 mg/L（=10 μg/mL）未満

＃＃： 国内臨床試験における再燃の基準（以下の 1～2 をすべて満たす場合）

臨床的再燃

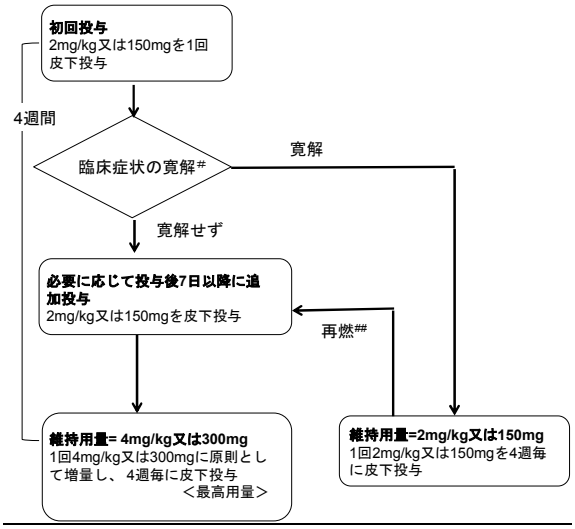
1．医師による自己炎症性疾患活動性の総合評価[注 2)] が軽度以上，又は医師による自己炎症性疾患活動性の総合評価[注 2)] が軽微かつ皮膚疾患の評価[注 2)] が軽度以上

血清学的再燃

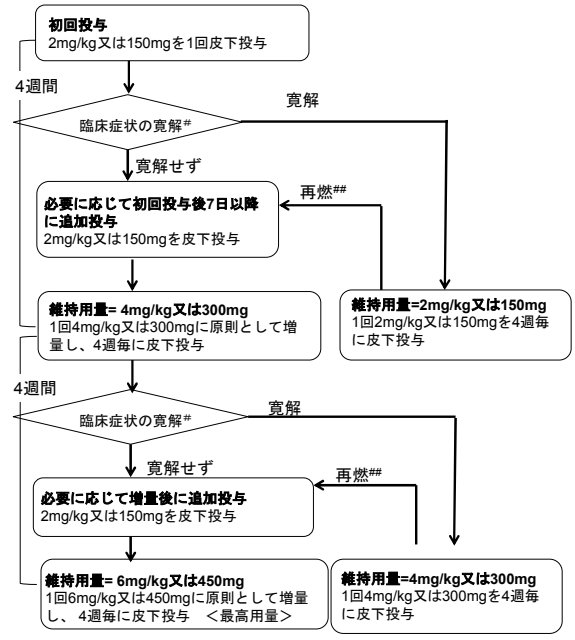
2．CRP が 30 mg/L（=3 mg/dL）超又は SAA が 30 mg/L（=30 μg/mL）超

注 2）評価基準：なし，軽微，軽度，中等度，重度の 5 段階

家族性地中海熱及び TNF 受容体関連周期性症候群の場合



メバロン酸キナーゼ欠損症／高 IgD 症候群の場合



＃：国際共同治験における寛解の基準：ランダム化時に認められた最初の再燃を index flare とし，投与 14 日後に以下の 2 つの条件を満たした場合，index flare の寛解とした。

- 臨床的寛解：医師による全般評価[注)] が軽微以下
- 血清学的寛解：CRP が 10 mg/L 以下未満又はベースラインと比べ 70%以上の減少

＃＃：国際共同治験における再燃の基準（以下の 1～2 をすべて満たす場合）

臨床的再燃

1. 医師による自己炎症性疾患活動性の総合評価[注)]が軽度以上 血清学的再燃 2. CRP が 30 mg/L（=3 mg/dL）以上 注）評価基準：なし，軽微，軽度，中等度，重度の 5 段階

2.4 用法及び用量に関連する使用上の注意の設定根拠

（1），（2）については，既承認事項と注意喚起すべき事項は共通しているため，現行の添付文書から変更していない。また，十分な臨床的効果が見られない場合の漸増方法について，CAPS の場合の概略図は変更していない。

十分な臨床的効果が見られない場合の漸増方法について，CAPS，FMF と TRAPS，MKD/HIDS で使用方法が異なるため，より分かりやすくする目的で各用法用量に合わせた図を掲載した。FMF と TRAPS，MKD/HIDS の寛解及び再燃の基準は，N2301 試験で使用された基準と同じものを採用している。

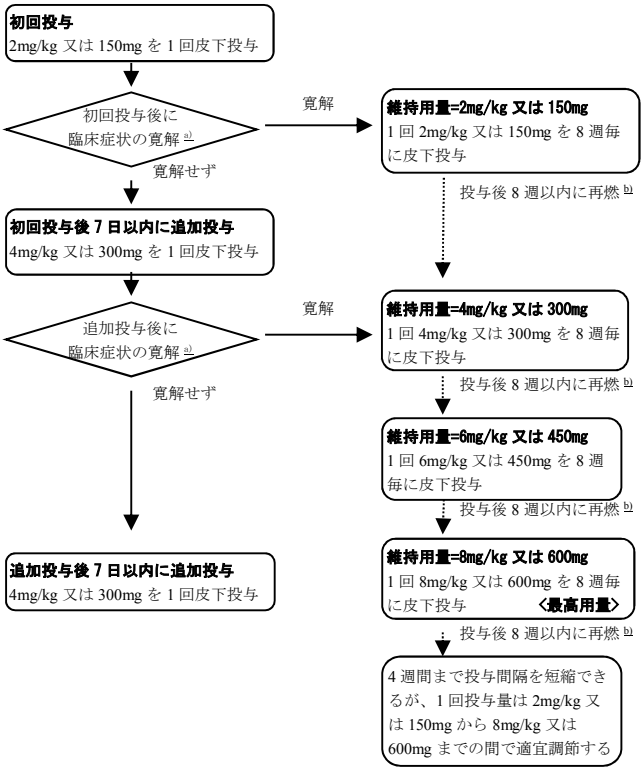
なお，審査中の独立行政法人医薬品医療機器総合機構との協議内容を踏まえ，用法及び用量に関連する使用上の注意（案）を以下の通り変更した。

＜用法及び用量に関連する使用上の注意（案）＞

⑴ 本剤 1 バイアルを日局注射用水 1.0mL に溶解した場合、溶液 1.0mL がカナキヌマブ（遺伝子組換え）の投与量 150mg に相当する。（「8．適用上の注意」の項参照）

⑵ 本剤の至適用量は患者の体重及び臨床症状によって異なり、投与量は患者毎に設定する必要がある。投与は 1 回 2mg/kg 又は 150mg の低用量から開始し、十分な効果がみられない、もしくは再燃がみられた場合に限り、下表を参考に投与量の増量を行うこと。

十分な臨床的効果がみられない場合の漸増方法
クリオピリン関連周期性症候群の場合



a)臨床試験における寛解の基準（以下の 1～3 をすべて満たす場合）

＜臨床的寛解＞

1．医師による自己炎症性疾患活動性の総合評価[注 2)] が軽微以下

2．皮膚疾患の評価[注 2)] が軽微以下

＜血清学的寛解＞

3． CRP が 10mg/L（=1mg/dL）未満又は SAA が 10mg/L（=10μg/mL）未満

b)臨床試験における再燃の基準（以下の 1～2 をすべて満たす場合）

＜臨床的再燃＞

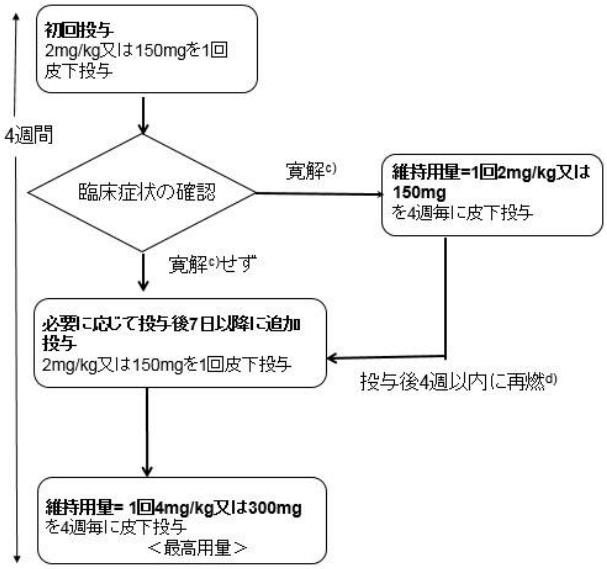
1．医師による自己炎症性疾患活動性の総合評価[注 2)] が軽度以上、又は医師による自己炎症性疾患活動性の総合評価[注 2)] が軽微かつ皮膚疾患の評価[注 2)] が軽度以上

＜血清学的再燃＞

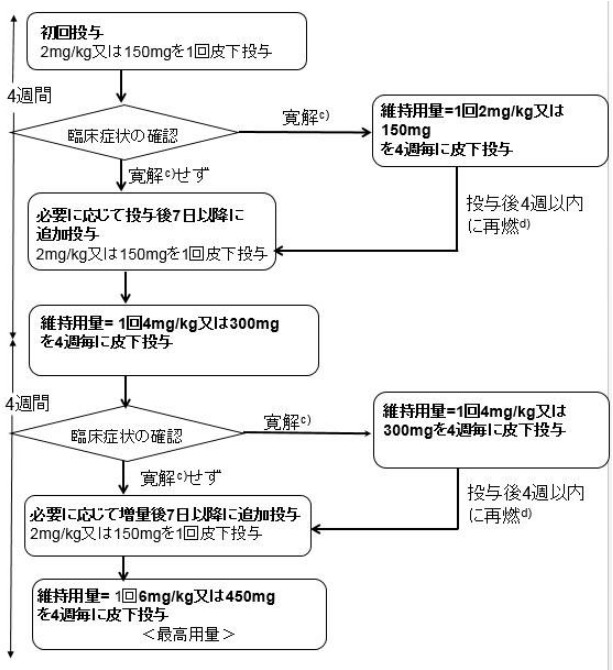
2．CRP が 30mg/L（=3mg/dL）超又は SAA が 30mg/L（=30μg/mL）超

注2) 評価基準：なし、軽微、軽度、中等度、重度の 5 段階

家族性地中海熱及び TNF 受容体関連周期性症候群の場合



高 IgD 症候群（メバロン酸キナーゼ欠損症）の場合



c) 臨床試験における寛解の基準

（以下の 1～2 をすべて満たす場合）

＜臨床的寛解＞

1.医師による自己炎症性疾患活動性の総合評価 注 3) が軽微以下

＜血清学的寛解＞

2.CRP が 10 mg/L 以下又はベースラインと比べ 70%以上の減少

d): 臨床試験における再燃の基準

（以下の 1～2 をすべて満たす場合）

＜臨床的再燃＞

１．医師による自己炎症性疾患活動性の総合評価注 3) が軽度以上

＜血清学的再燃＞

２．CRP が 30mg/L（=3mg/dL）以上

注 3）評価基準：なし、軽微、軽度、中等度、重度の 5 段階

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1.8.3 使用上の注意（案）及びその設定根拠

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イラリス皮下注用 150 mg の使用上の注意（案）は，現行のイラリス皮下注用 150 mg の添付文書（第 5 版，2015 年 3 月改訂）を基に，家族性地中海熱患者，TNF 受容体関連周期性症候群患者，

高 IgD 症候群（メバロン酸キナーゼ欠損症）患者を対象とした国際共同試験（N2301 試験）の安全性の結果（16 週中間集計の結果：各被験者の二重盲検期までのデータ）及び Core Data Sheet (CDS)Version[redacted]（20[redacted]年[redacted]月[redacted]日改訂）を基に設定した。

1 警告欄

1.1 警告

【警告】

1. 本剤投与により，敗血症を含む重篤な感染症等があらわれることがあり，本剤との関連性は明らかではないが，悪性腫瘍の発現も報告されている。本剤が疾病を完治させる薬剤でないことも含め，これらの情報を患者に十分説明し，患者が理解したことを確認した上で，治療上の有益性が危険性を上回ると判断される場合にのみ本剤を投与すること。また，本剤の投与において，重篤な感染症等の副作用により，致命的な経過をたどることがあるので，緊急時に十分に措置できる医療施設及び医師のもとで投与し，本剤投与後に副作用が発現した場合には，速やかに担当医に連絡するよう患者に注意を与えること。

2. 敗血症等の致命的な感染症が報告されているため，十分な観察を行うなど感染症の発現に注意すること。

3. 本剤及びクリオピリン関連周期性症候群，家族性地中海熱，TNF 受容体関連周期性症候群又は高 IgD 症候群（メバロン酸キナーゼ欠損症）について十分な知識をもつ医師が使用すること。

1.2 警告の設定根拠

1. 現行のイラリス皮下注用 150 mg の添付文書（第 5 版）に記載されている内容について，変更を要する追加情報は得られていないことから，イラリス皮下注用 150 mg の添付文書（第 5 版）に基づき設定した。
2. 1 に同じ。
3. 本剤及び本剤の適応症である，クリオピリン関連周期性症候群，家族性地中海熱，TNF 受容体関連周期性症候群又は高 IgD 症候群（メバロン酸キナーゼ欠損症）について 十分な知識をもつ医師によって本剤が使用されるよう，注意として設定した。

2 禁忌欄

2.1 禁忌

【禁忌（次の患者には投与しないこと）】

1. 重篤な感染症の患者〔感染症が悪化するおそれがある。〕
2. 活動性結核の患者〔症状が悪化するおそれがある。〕
3. 本剤の成分に対し過敏症の既往歴のある患者

2.2 禁忌の設定根拠

現行のイラリス皮下注用 150 mg の添付文書（第 5 版）に記載されている内容について，変更を要する追加情報は得られていないことから，イラリス皮下注用 150 mg の添付文書（第 5 版）に基づき設定した。

3 慎重投与欄

3.1 慎重投与

(次の患者には慎重に投与すること)

1. 感染症の患者又は感染症が疑われる患者〔感染症が悪化するおそれがある。〕（「2. 重要な基本的注意」の項参照）
2. 結核の既往歴を有する患者又は結核感染が疑われる患者〔結核を活動化させるおそれがある。〕（「2. 重要な基本的注意」の項参照）
3. 再発性感染症の既往歴のある患者〔感染症が再発するおそれがある。〕（「2. 重要な基本的注意」の項参照）
4. 易感染性の状態にある患者〔感染症を誘発するおそれがある。〕

3.2 慎重投与の設定根拠

現行のイラリス皮下注用 150 mg の添付文書（第 5 版）に記載されている内容について，変更を要する追加情報は得られていないことから，イラリス皮下注用 150 mg の添付文書（第 5 版）に基づき設定した。

4 重要な基本的注意欄

4.1 重要な基本的注意

1. 臨床試験において，上気道感染等の感染症が高頻度に報告されており，重篤な感染症も報告されているため，本剤投与中は感染症の発現，再発及び増悪に十分注意すること。（「4. 副作用⑴重大な副作用」の項参照）
2. 本剤により感染に対する炎症反応が抑制される可能性があるため，本剤投与中は患者の状態を十分に観察すること。

3. 本剤投与に先立って結核に関する十分な問診及び胸部 X 線（レントゲン）検査に加えインターフェロンγ遊離試験又はツベルクリン反応検査を行い，適宜胸部 CT 検査等を行うことにより，結核感染の有無を確認すること。結核の既往歴を有する場合及び結核感染が疑われる場合には，結核の診療経験がある医師に相談すること。以下のいずれかの患者には，原則として抗結核薬を投与した上で，本剤を投与すること。
   1) 胸部画像検査で陳旧性結核に合致するか推定される陰影を有する患者
   2) 結核の治療歴（肺外結核を含む）を有する患者
   3) インターフェロンγ遊離試験やツベルクリン反応検査等の検査により，既感染が強く疑われる患者
   4) 結核患者との濃厚接触歴を有する患者

   また，本剤投与中も，胸部 X 線検査等の適切な検査を定期的に行うなど結核症の発現には十分に注意し，患者に対し，結核を疑う症状（持続する咳，体重減少，発熱等）が発現した場合には速やかに担当医に連絡するよう説明すること。なお，結核の活動性が確認された場合は結核の治療を優先し，本剤を投与しないこと。
4. 本剤投与により好中球減少があらわれることがあるので，初回投与前，概ね投与 1 ヵ月後，及びその後本剤投与中は定期的に好中球数を測定すること。（「4. 副作用⑴重大な副作用」の項参照）
5. 臨床試験において，アナフィラキシー又はアナフィラキシーショックは報告されていないが，本剤の投与に対する過敏症反応が報告されているため，重篤な過敏症反応のリスクを除外することはできない。本剤を投与する際には過敏症反応の発現に注意し，必要に応じて適切な処置を行うこと。
6. 本剤を投与された患者において，悪性腫瘍が報告されている。本剤を含む抗 IL-1 製剤との関連性は明らかではないが，悪性腫瘍等の発現には注意すること。
7. 本剤投与中は，生ワクチン接種による感染症発現のリスクを否定できないため，生ワクチン接種は行わないこと。本剤投与前に，必要なワクチンを接種しておくことが望ましい。
8. 本剤は，マスターセルバンク及びワーキングセルバンク作製時において，培地成分の一部としてヒト血清アルブミン及びヒト血清トランスフェリンを使用しているが，最終製品の成分としては含まれていない。これらヒト血液由来成分のうち，ヒト血清アルブミンの原血漿に対して C 型肝炎ウイルス（HCV）に対する核酸増幅検査を実施している。原血漿を対象としたその他の核酸増幅検査は実施していないが，血清学的検査によりウイルスの抗原又はウイルスに対する抗体が陰性であることを確認している。更に，これらヒト血液由来成分及びカナキヌマブ（遺伝子組換え）の製造において，複数の工程によりウイルスの除去・不活化をしており，最終製品への B 型肝炎ウイルス（HBV），C 型肝炎ウイルス（HCV）及びヒト免疫不全ウイルス（HIV-1 及び HIV-2）混入の可能性は

極めて低い。また，ヒト血清アルブミンの製造にオランダで採血したヒト血液を用いているが，本剤の投与により伝達性海綿状脳症（TSE）がヒトに伝播したとの報告はなく，TSE に関する理論的なリスク評価値は，一定の安全性を確保する目安に達しており，本剤による TSE 伝播のリスクは極めて低い。本剤の投与に際しては，その旨の患者又はその保護者への説明を考慮すること。

4.2 重要な基本的注意の設定根拠

現行のイラリス皮下注用 150 mg の添付文書（第 5 版）に記載されている内容について，変更を要する追加情報は得られていないことから，イラリス皮下注用 150 mg の添付文書（第 5 版）に基づき設定した。

なお，1 及び 5 の注意については，クリオピリン関連周期性症候群の海外臨床試験について記載していたが，家族性地中海熱患者，TNF 受容体関連周期性症候群患者，高 IgD 症候群（メバロン酸キナーゼ欠損症）患者を対象とした国際共同試験（N2301 試験）の安全性も検討した上での記載となるため，「臨床試験において」と記載を整備した。

また，5 の注意については，「医薬品・医療機器等安全性情報 No.299 参考資料副作用名「アナフィラキシー」について」に従い，従来記載していた「アナフィラキシー様症状」を「アナフィラキシー」に記載整備した。

5 相互作用欄

5.1 相互作用

本剤と他の薬剤との相互作用を検討した臨床試験は実施されていない。

代謝酵素チトクローム P450（CYP450）の発現は，IL-1β 等の炎症性サイトカインにより抑制されているとの報告があり，本剤の IL-1β 阻害作用により，CYP450 の発現が増加する可能性がある。CYP450 により代謝され，治療域が狭い薬剤と併用する場合には，これらの薬剤の効果や血中濃度に関するモニタリングを行い，必要に応じて投与量を調節すること。

併用注意 （併用に注意すること）

薬剤名等	臨床症状・措置方法	機序・危険因子
抗 TNF 製剤	重篤な感染症発現のリスクが増大するおそれがある。また，他の抗 IL-1 製剤と抗 TNF 製剤との併用により，重篤な感染症の発現頻度増加が認められているため，本剤との併用は行わないことが望ましい。	共に免疫抑制作用を有するため。

5.2 相互作用の設定根拠

現行のイラリス皮下注用 150 mg の添付文書（第 5 版）に記載されている内容について，変更を要する追加情報は得られていないことから，イラリス皮下注用 150 mg の添付文書（第 5 版）に基づき設定した。

6 副作用欄

6.1 副作用

クリオピリン関連周期性症候群患者の国内臨床試験（D2308 試験）において，19 例中 12 例（63.2%）に副作用が認められた。主な副作用は鼻咽頭炎 3 例（15.8%），口内炎 2 例（10.5%）等であった。

クリオピリン関連周期性症候群患者の海外臨床試験（A2102 試験，D2304 試験，D2306 試験の併合解析）において，169 例中 68 例（40.2%）に副作用が認められた。主な副作用は頭痛 7 例（4.1%），体重増加 7 例（4.1%），回転性めまい 6 例（3.6%），気管支炎 5 例（3.0%）等であった。（承認時までの集計）

家族性地中海熱患者，TNF 受容体関連周期性症候群患者，高 IgD 症候群（メバロン酸キナーゼ欠損症）患者の国際共同試験（N2301 試験）において，169 例(日本人 8 例を含む)中 47 例（27.8%）に副作用が認められた。主な副作用は注射部位反応 13 例（7.7%），頭痛 5 例（3.0%）等であった。（承認時までの集計）
「重大な副作用」及び「その他の副作用」について，クリオピリン関連周期性症候群患者の国内臨床試験及び家族性地中海熱患者，TNF 受容体関連周期性症候群患者，高 IgD 症候群（メバロン酸キナーゼ欠損症）患者の国際共同試験における日本人患者で認められなかった副作用は頻度不明とした。

(1) 重大な副作用

1) 重篤な感染症（6.7%）：敗血症や日和見感染症（アスペルギルス症，非定型抗酸菌症，帯状疱疹等）等の重篤な感染症があらわれることがあるので，本剤投与後は患者の状態を十分に観察し，異常が認められた場合には感染症に対する治療を行い，本剤の投与は継続しないこと。

2) 好中球減少（頻度不明）：好中球減少があらわれることがあるので，定期的に血液検査を実施するなど観察を十分に行い，異常が認められた場合には投与を中止するなど，適切な処置を行うこと。

(2) その他の副作用

	頻度不明	5%以上	5%未満
感染症	尿路感染，気管支炎，ウイルス感染，扁桃炎，鼻炎，耳感染，咽頭炎，外陰部膣カンジダ症，下気道感染，肺感染	鼻咽頭炎	胃腸炎，肺炎，副鼻腔炎，上気道感染

神経系	回転性めまい	-	頭痛
過敏症	過敏症反応	-	-
皮膚	-	-	注射部位反応
消化器	下痢	口内炎	-
肝臓	AST（GOT）・ALT（GPT）上昇	-	-
その他	体重増加，血小板数減少	-	-

6.2 副作用の設定根拠

現行のイラリス皮下注用 150 mg の添付文書（第 5 版）に記載されている内容に加え，家族性地中海熱患者，TNF 受容体関連周期性症候群患者，高 IgD 症候群（メバロン酸キナーゼ欠損症）患者を対象とした国際共同試験（N2301 試験）における 16 週間までの副作用の発現状況の概要を追記した。

「重大な副作用」の項については，現行のイラリス皮下注用 150 mg の添付文書（第 5 版）に記載されている内容について，変更を要する追加情報は得られていないことから，イラリス皮下注用 150 mg の添付文書（第 5 版）に基づき設定した。

「その他の副作用」の項については，現行のイラリス皮下注用 150 mg の添付文書 2015 年 3 月改訂（第 5 版）に記載されている副作用に加え，N2301 試験を基に CDS に追記された事象のうち現行添付文書に記載されていないものを追記した。（扁桃炎，鼻炎，耳感染，咽頭炎，外陰部膣カンジダ症，下気道感染，肺感染，胃腸炎，肺炎，副鼻腔炎，血小板数減少）

なお，「重大な副作用」及び「その他の副作用」の発現頻度は，クリオピリン関連周期性症候群患者の国内臨床試験における発現頻度及び家族性地中海熱患者，TNF 受容体関連周期性症候群患者，高 IgD 症候群（メバロン酸キナーゼ欠損症）患者の国際共同試験における日本人患者での発現頻度（16 週間までのデータ）に基づき記載した。また，これらの患者において認められていない副作用については頻度不明とした。

7 高齢者への投与欄

7.1 高齢者への投与

一般に高齢者では生理機能が低下しているので注意すること。

7.2 高齢者への投与の設定根拠

現行のイラリス皮下注用 150 mg の添付文書（第 5 版）に記載されている内容について，変更を要する追加情報は得られていないことから，イラリス皮下注用 150 mg の添付文書（第 5 版）に基づき設定した。

8 妊婦，産婦，授乳婦等への投与欄

8.1 妊婦，産婦，授乳婦等への投与

1. 妊婦又は妊娠している可能性のある婦人には，治療上の有益性が危険性を上回ると判断される場合にのみ投与すること。〔妊娠中の投与に関する安全性は確立していない。動物実験（マーモセット）で胎児への移行が認められている。〕
2. 授乳婦に投与する場合には，授乳を中止させること。〔動物実験（マウス）でマウス抗マウス IL-1β 抗体を母動物に授乳期まで投与した際，マウス新生児に同抗体が移行したとの報告がある。〕

8.2 妊婦，産婦，授乳婦等への投与の設定根拠

現行のイラリス皮下注用 150 mg の添付文書（第 5 版）に記載されている内容について，変更を要する追加情報は得られていないことから，イラリス皮下注用 150 mg の添付文書（第 5 版）に基づき設定した。

9 小児等への投与欄

9.1 小児等への投与

低出生体重児，新生児，乳児又は 2 歳未満の幼児に対する，安全性及び有効性は確立していない。（使用経験がない。）

9.2 小児等への投与の設定根拠

現行のイラリス皮下注用 150 mg の添付文書（第 5 版）に記載されている内容について，変更を要する追加情報は得られていないことから，イラリス皮下注用 150 mg の添付文書（第 5 版）に基づき設定した。

10 適用上の注意欄

10.1 適用上の注意

1. 投与経路

本剤の投与は皮下投与のみとすること。

2. 調製前の準備

巻末の投与液量一覧表を参考に，必要数のバイアル，日局注射用水注入用注射筒（1 mL），投与用注射筒（必要液量を正確に採取できる注射筒）及び注射針（21 ゲージ及び 27 ゲージ）を用意すること。

3. 調製方法

1）本剤は泡立ちやすいので，調製する際は，バイアルを振らない等，注意すること。
2）本剤の溶解には日局注射用水以外は使用しないこと。
3）バイアルのゴム栓部分をアルコール綿等で消毒する。
4）**21 ゲージ**の注射針を装着した 1 mL の注射筒を用いて，本剤 1 バイアルに日局注射用水 **1.0 mL** をゆっくりと注入して溶解する（**液量は 1.2 mL となる**）。
5）約 45°の角度でバイアルを約 1 分間ゆっくりと回転させた後，5 分間静置する。
6）バイアルをゆっくりと 10 回上下反転させる。可能であれば，指でゴム栓に触れないようにする。このときバイアルを振らないこと。
7）室温で約 15 分間静置する。
8）バイアルの側面を軽く叩き，ゴム栓に付着している液体を下に移動させる。この溶液には肉眼で確認できる粒子はほとんど含まれておらず，澄明又は混濁している。
9）溶解後 60 分以内に使用しない場合は，冷蔵庫内（2～8°C）で保管し，24 時間以内に使用すること。使用後の残液は使用しないこと。

4. 投与時

1）溶液内に粒子がある場合等，外観に異常を認めた場合には使用しないこと。
2）**本剤 1 バイアルを日局注射用水 1.0 mL に溶解した場合，溶液 1.0 mL がカナキヌマブ（遺伝子組換え）の投与量 150 mg に相当する**。投与量に応じて必要な液量を，**21 ゲージ**の注射針を装着した注射筒を用いて注意深く採取する。このとき，必要液量を正確に採取できる注射筒を用いること。
3）採取後，**27 ゲージ**の注射針を用いて皮下投与する。
4）瘢痕組織への投与を避けること。
5）1 回につき 1.0 mL を超えて投与する場合には，1 箇所あたり 1.0 mL を超えないように部位を分けて投与すること。

10.2 適用上の注意の設定根拠

現行のイラリス皮下注用 150 mg の添付文書（第 5 版）に記載されている内容について，変更を要する追加情報は得られていないことから，イラリス皮下注用 150 mg の添付文書（第 5 版）に基づき設定した。

11 その他の注意欄

11.1 その他の注意

1. クリオピリン関連周期性症候群患者を対象とした国内及び海外臨床試験において，白血球数及び血小板数の平均値が減少したが，これらの変動は炎症反応の低下による可能性がある。
2. クリオピリン関連周期性症候群患者を対象とした海外臨床試験において，トランスアミナーゼ上昇を伴わない，無症候性で軽度の血清ビリルビン上昇が報告されている。

11.2 その他の注意の設定根拠

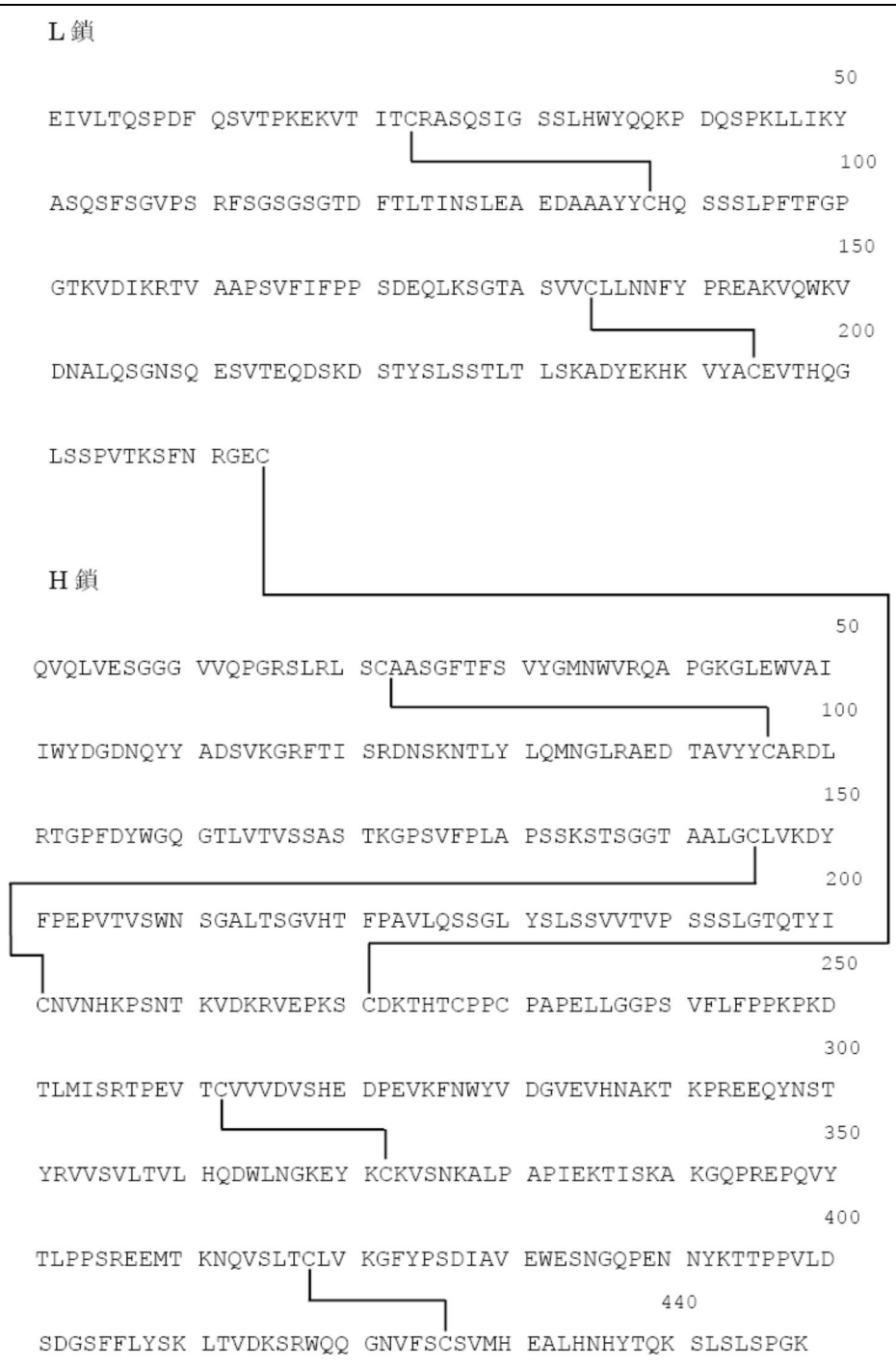
現行のイラリス皮下注用 150 mg の添付文書（第 5 版）に記載されている内容について，変更を要する追加情報は得られていないことから，イラリス皮下注用 150 mg の添付文書（第 5 版）に基づき設定した。

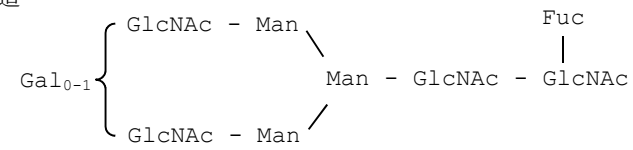
1.9 一般的名称に係る文書

既承認医薬品に係る資料を参照

1.10 毒薬・劇薬等の指定審査資料のまとめ

＜現行＞

化学名・別名	カナキヌマブは，ヒトインターロイキン-1ß に対する遺伝子組換えヒト IgG1 モノクローナル抗体である。 カナキヌマブは，マウスハイブリドーマ細胞 Sp2/0-Ag14 で産生される。 カナキヌマブは，448 個のアミノ酸残基からなる H 鎖（γ1 鎖）2 分子及び 214 個のアミノ酸残基からなる L 鎖（κ 鎖）2 分子で構成される糖タンパク質（分子量：約 148,000）である。
構造式	 H 鎖 Q1：ピログルタミン酸， K448：部分的プロセシング

<table>
<tr><td></td><td>N298：糖鎖結合部位
主糖鎖構造

分子内ジスルフィド結合
L 鎖 C23-L 鎖 C88，L 鎖 C134-L 鎖 C194，H 鎖 C22-H 鎖 C96，H 鎖 C145-H 鎖 C201，
H 鎖 C262-H 鎖 C322，H 鎖 C368-H 鎖 C426
分子間ジスルフィド結合
L 鎖 C214-H 鎖 C221，H 鎖 C227-H 鎖 C227，H 鎖 C230-H 鎖 C230</td></tr>
<tr><td>効能・効果</td><td>以下のクリオピリン関連周期性症候群
・家族性寒冷自己炎症症候群
・マックル・ウェルズ症候群
・新生児期発症多臓器系炎症性疾患</td></tr>
<tr><td>用法・用量</td><td>通常，体重 40 kg 以下の患者にはカナキヌマブ(遺伝子組換え)として 1 回 2 mg/kg を，体重 40 kg を超える患者には 1 回 150 mg を 8 週毎に皮下投与する。
十分な臨床的効果（皮疹及び炎症症状の寛解）がみられない場合には適宜漸増するが，1 回最高用量は体重 40 kg 以下の患者では 8 mg/kg，体重 40 kg を超える患者では 600 mg とする。
最高用量まで増量し，8 週以内に再燃がみられた場合には，投与間隔を 4 週間まで短縮できる。
なお，症状に応じて 1 回投与量の増減を検討すること。</td></tr>
<tr><td>劇薬等の指定</td><td></td></tr>
<tr><td>市販名及び有効成分・分量</td><td>原体：カナキヌマブ（遺伝子組換え）
製剤：イラリス皮下注用 150 mg
［1 バイアル中の含有量：カナキヌマブ（遺伝子組換え）180.0 mg］
［日本薬局方「注射用水」1.0 mL で溶解した溶液 1.0 mL に含まれる量：カナキヌマブ（遺伝子組換え）150.0 mg］</td></tr>
<tr><td>毒性</td><td>単回投与毒性試験
<table>
<tr><td>動物種</td><td>静脈内</td><td>皮下</td></tr>
<tr><td>マーモセット ♂♀</td><td>100 mg/kg まで死亡はみられず</td><td>150 mg/kg まで死亡はみられず</td></tr>
</table>
単回投与毒性試験は実施していないため，反復投与毒性試験の結果から記載した。

反復投与毒性試験
<table>
<tr><td>動物種</td><td>投与期間</td><td>投与経路</td><td>投与量 (mg/kg)</td><td>無毒性量 (mg/kg)</td><td>主な所見</td></tr>
<tr><td>マーモセット</td><td>試験 1 日及び 43 日</td><td>皮下</td><td>5，50 及び 150</td><td>150</td><td>カナキヌマブの投与に起因した毒性所見なし</td></tr>
<tr><td>マーモセット</td><td>13 週間，週 2 回</td><td>皮下</td><td>15，50 及び 150</td><td>150</td><td>カナキヌマブの投与に起因した毒性所見なし</td></tr>
<tr><td>マーモセット</td><td>28 日間，週 2 回</td><td>静脈内</td><td>10，30 及び 100</td><td>100</td><td>カナキヌマブの投与に起因した毒性所見なし</td></tr>
<tr><td>マーモセット</td><td>26 週間，週 2 回</td><td>静脈内</td><td>10，30 及び 100</td><td>100</td><td>カナキヌマブの投与に起因した毒性所見なし</td></tr>
</table></td></tr>
</table>

副　作　用	【国内臨床試験結果】 副作用発現率　12/19 = 63.2% 主な副作用の種類　件数 鼻咽頭炎 Nasopharyngitis　3 口内炎 Stomatitis　2 【海外 CAPS 対象臨床試験結果併合集計】 副作用発現率　68/169 = 40.2% 主な副作用の種類　件数 体重増加 Weight increased　7 頭痛 headache　7 回転性めまい vertigo　6 気管支炎 Bronchitis　5
会　　社	ノバルティス ファーマ株式会社　製剤：製造販売（輸入）

＜追加・変更＞（下線部）

化学名・別名	
構造式	
効能・効果	1. 以下のクリオピリン関連周期性症候群 • 家族性寒冷自己炎症症候群 • マックル・ウェルズ症候群 • 新生児期発症多臓器系炎症性疾患 2. 既存治療で効果不十分な家族性地中海熱 3. TNF 受容体関連周期性症候群 4. 高 IgD 症候群（メバロン酸キナーゼ欠損症）
用法・用量	1. クリオピリン関連周期性症候群 通常、体重 40 kg 以下の患者にはカナキヌマブ（遺伝子組換え）として 1 回 2 mg/kg を、体重 40 kg を超える患者には 1 回 150 mg を 8 週毎に皮下投与する。 十分な臨床的効果（皮疹及び炎症症状の寛解）がみられない場合には適宜漸増するが、1 回最高用量は体重 40 kg 以下の患者では 8 mg/kg、体重 40 kg を超える患者では 600 mg とする。 最高用量まで増量し、8 週以内に再燃がみられた場合には、投与間隔を 4 週間まで短縮できる。 なお、症状に応じて 1 回投与量の増減を検討すること。 2. 家族性地中海熱及び TNF 受容体関連周期性症候群 通常、体重 40 kg 以下の患者にはカナキヌマブ（遺伝子組換え）として 1 回 2 mg/kg を、体重 40 kg を超える患者には 1 回 150 mg を、4 週毎に皮下投与する。 十分な臨床的効果がみられない場合には追加投与又は適宜漸増するが、1 回最高用量は体重 40 kg 以下の患者では 4 mg/kg、体重 40 kg を超える患者では 300 mg とする。 3. 高 IgD 症候群（メバロン酸キナーゼ欠損症） 通常、体重 40 kg 以下の患者にはカナキヌマブ（遺伝子組換え）として 1 回 2 mg/kg を、体重 40 kg を超える患者には 1 回 150 mg を、4 週毎に皮下投与する。 十分な臨床的効果がみられない場合には追加投与又は適宜漸増するが、1 回最高用量は体重 40 kg 以下の患者では 6 mg/kg、体重 40 kg を超える患者では 450 mg とする。
劇薬等の指定	
市販名及び有効成分・分量	
毒性	
副作用	【クリオピリン関連周期性症候群患者対象の国内臨床試験】 副作用発現率　12/19 = 63.2% 主な副作用の種類　例数 鼻咽頭炎　3 口内炎　2 【海外クリオピリン関連周期性症候群患者対象臨床試験結果併合集計】 副作用発現率　68/169 = 40.2% 主な副作用の種類　例数 体重増加　7 頭痛　7 回転性めまい　6 気管支炎　5

	【家族性地中海熱患者，TNF 受容体関連周期性症候群患者，高 IgD 症候群（メバロン酸キナーゼ欠損症）患者対象国際共同治験】 副作用発現率　47/169（日本人 8 例含む）＝27.8% 主な副作用の種類　例数 注射部位反応　13 頭痛　5
会　社	

1.12 添付資料一覧

目　　次

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1　第 3 部 3
2　第 4 部 4
3　第 5 部 6

1 第 3 部

該当資料なし

添付資料番号	著者・表 題・掲載誌	報種類（国内／海外）
4.3 参考文献 （評価／参考の別：参考資料）		
4.3-1	Aksentijevich I and Kastner DL (2011) Genetics of monogenic autoinflammatory diseases: past successes, future challenges. Nat Rev Rheumatol; 7(8):469-78.	海外
4.3-2	Bodar EJ, Kuijk LM, Drenth JP, et al. (2011) On-demand anakinra treatment is effective in mevalonate kinase deficiency. Ann Rheum Dis; 70(12):2155-8.	海外
4.3-3	Bulua AC, Simon A, Maddipati R, et al. (2011) Mitochondrial reactive oxygen species promote production of proinflammatory cytokines and are elevated in TNFR1-associated periodic syndrome (TRAPS). J Exp Med; 208(3):519-33.	海外
4.3-4	Chae JJ, Wood G, Masters SL, et al. (2006) The B30.2 domain of pyrin, the familial Mediterranean fever protein, interacts directly with caspase-1 to modulate IL-1beta production. Proc Natl Acad Sci USA; 103(26):9982-7.	海外
4.3-5	Chae JJ, Cho YH, Lee GS, et al. (2011) Gain-of-function Pyrin mutations induce NLRP3 protein-independent interleukin-1β activation and severe autoinflammation in mice. Immunity; 34(5):755-68.	海外
4.3-6	Elkordy M, Crump M, Vredenburgh JJ, et al. (1997) A phase I trial of recombinant human interleukin-1β (OCT-43) following high-dose chemotherapy and autologous bone marrow transplantation. Bone Marrow Transplant; 19(4):315-22.	海外
4.3-7	Eroglu FK, Beşbaş N, Topaloglu R, et al. (2015) Treatment of colchicine-resistant Familial Mediterranean fever in children and adolescents. Rheumatol Int; 35(10):1733-7.	海外
4.3-8	Fairclough LC, Stoop AA, Negm OH, et al. (2015) Tumour necrosis factor receptor I blockade shows that TNF-dependent and TNF-independent mechanisms synergise in TNF receptor associated periodic syndrome. Eur J Immunol; 45(10):2937-44.	海外
4.3-9	Galeotti C, Meinzer U, Quartier P, et al. (2012) Efficacy of interleukin-1-targeting drugs in mevalonate kinase deficiency. Rheumatology (Oxford); 51(10):1855-9.	海外
4.3-10	Gattorno M, Obici L, Meini A, et al. (2012) Efficacy and Safety of Canakinumab in Patients with TNF Receptor Associated Periodic Syndrome. Arthritis Rheum; 64(s10):s322.	海外
4.3-11	Greco E, Aita A, Galozzi P, et al. (2015) The novel S59P mutation in the TNFRSF1A gene identified in an adult onset TNF receptor associated periodic syndrome (TRAPS) constitutively activates NF-κB pathway. Arthritis Res Ther; 17:93.	海外
4.3-12	Gül A, Ozdogan H, Erer B, et al. (2015) Efficacy and safety of canakinumab in adolescents and adults with colchicine-resistant familial Mediterranean fever. Arthritis Res Ther; 17(1):243.	海外
4.3-13	Holzinger D, Kessel C, Omenetti A, et al. (2015) From bench to bedside and back again: translational research in autoinflammation. Nat Rev Rheumatol; 11(10):573-85.	海外
4.3-14	Kimberley FC, Lobito AA, Siegel RM, et al. (2007) Falling into TRAPS - receptor misfolding in the TNF receptor 1-associated periodic fever syndrome. Arthritis Res Ther; 9(4):217.	海外
4.3-15	Leung YY, Yao Hui LL, Kraus VB (2015) Colchicine - Update on mechanisms of action and therapeutic uses. Semin Arthritis Rheum; 45(3):341-50.	海外
4.3-16	Marcuzzi A, Zanin V, Kleiner G, et al. (2013) Mouse model of mevalonate kinase deficiency: comparison of cytokine and chemokine profile with that of human patients. Pediatr Res; 1-6.	海外
4.3-17	Martínez GJ, Robertson S, Barraclough J, et al. (2015) Colchicine Acutely Suppresses Local Cardiac Production of Inflammatory Cytokines in Patients With an Acute Coronary Syndrome. J Am Heart Assoc; 4(8):1-10.	海外
4.3-18	Massonnet B, Normand S, Moschitz R, et al. (2009) Pharmacological inhibitors of the mevalonate pathway activate pro-IL-1 processing and IL-1 release by human monocytes. Eur Cytokine Netw; 20(3):112-20.	海外

添付資料番号	著者・表 題・掲載誌	報種類（国内／海外）
4.3-19	Meinzer U, Quartier P, Alexandra JF, et al. (2011) Interleukin-1 targeting drugs in familial Mediterranean fever: a case series and a review of the literature. Semin Arthritis Rheum; 41(2):265-71.	海外
4.3-20	Normand S, Massonnet B, Delwail A, et al. (2009) Specific increase in caspase-1 activity and secretion of IL-1 family cytokines: a putative link between mevalonate kinase deficiency and inflammation. Eur Cytokine Netw; 20(3):101-7.	海外
4.3-21	Papin S, Cuenin S, Agostini L, et al. (2007) The SPRY domain of Pyrin, mutated in familial Mediterranean fever patients, interacts with inflammasome components and inhibits proIL-1beta processing. Cell Death Differ; 14(8):1457-66.	海外
4.3-22	Simon A, Park H, Maddipati R, et al. (2010) Concerted action of wild-type and mutant TNF receptors enhances inflammation in TNF receptor 1-associated periodic fever syndrome. Proc Natl Acad Sci USA; 107(21):9801-6.	海外
4.3-23	Stoffels M, Szperl A, Simon A, et al. (2014) MEFV mutations affecting pyrin amino acid 577 cause autosomal dominant autoinflammatory disease. Ann Rheum Dis; 73(2):455-61.	海外
4.3-24	ter Haar NM, Oswald M, Jeyaratnam J, et al. (2015) Recommendations for the management of autoinflammatory diseases. Ann Rheum Dis; 74(9):1636-44.	海外
4.3-25	Tufan A, Babaoglu MO, Akdogan A, et al. (2007) Association of drug transporter gene ABCB1 (MDR1) 3435C to T polymorphism with colchicine response in familial Mediterranean fever. J Rheumatol; 34(7):1540-4.	海外
4.3-26	van der Burgh R, ter Haar NM, Boes ML, et al. (2013) Mevalonate kinase deficiency, a metabolic autoinflammatory disease. Clin Immunol; 147(3):197-206.	海外

添付資料番号	表 題	著者	試験実施期間	試験実施場所	報種類（国内／海外）	掲載誌	評価／参考
5.2　全臨床試験一覧表							
5.2	全臨床試験一覧表	ノバルティス	－	－	国内	社内報告書	評価
5.3 試験報告書及び関連情報							
5.3.1　生物薬剤学試験報告書							
5.3.1.1　バイオアベイラビリティ（BA）試験報告書【該当資料なし】							
5.3.1.2　比較BA試験及び生物学的同等性（BE）試験報告書							
5.3.1.2-1	A randomized, open-label, single-dose, parallel-group study in healthy subjects to determine the bioequivalence of a liquid formulation of ACZ885 (canakinumab) with respect to the lyophilized form of ACZ885 following 150 mg subcutaneous administration	ノバルティス	2010年9月28日～2011年7月1日	米国，計3施設	海外	社内報告書	評価
5.3.1.3　*In Vitro*-*In Vivo* の関連を検討した試験報告書							
5.3.1.3-1	Comparability Report: From Powder for solution for injection to solution for injection	ノバルティス	2015年8月25日	_	海外	社内報告書	参考
5.3.1.4　生物学的及び理化学的分析法検討報告書							
5.3.1.4-1	Method transfer and cross-validation for the quantitative determination of ACZ885 in human serum by a competitive ELISA method	ノバルティス	2009年9月22日	フランス，計1施設	海外	社内報告書	参考
5.3.1.4-2	Quantitative determination of ACZ885 in human serum by ELISA Method Description and Validation	ノバルティス	2011年8月4日	フランス，計1施設	海外	社内報告書	参考
5.3.1.4-3	Quantitative determination of ACZ885 in human serum by ELISA Method Description and Validation Amendment No. 1	ノバルティス	2013年11月22日	フランス，計1施設	海外	社内報告書	参考
5.3.1.4-4	Method transfer and cross-validation for the quantitative determination of total IL-1 beta in human serum by an ELISA method	ノバルティス	2009年9月22日	フランス，計1施設	海外	社内報告書	参考
5.3.1.4-5	Determination of anti-ACZ885 antibodies in human serum by a homogeneous bridging immunogenicity assay on MSD Method description and validation	ノバルティス	2010年12月15日	スイス，計1施設	海外	社内報告書	参考
5.3.1.4-6	Transfer and validation of an immunogenicity method for the determination of anti-ACZ885 in human serum Method description and validation	ノバルティス	2011年7月4日	フランス，計1施設	海外	社内報告書	参考

添付資料番号	表 題	著者	試験実施期間	試験実施場所	報種類（国内／海外）	掲載誌	評価／参考
5.3.1.4-7	Transfer and validation of an immunogenicity method for the determination of anti-ACZ885 antibodies in human serum Method description and validation Amendment no. 1	ノバルティス	2012年10月11日	フランス，計1施設	海外	社内報告書	参考
5.3.1.4-8	Development and validation of an immunogenicity method with improved drug tolerance for the determination of anti-ACZ885 antibodies in human serum Method description and validation	ノバルティス	2014年9月25日	フランス，計1施設	海外	社内報告書	参考
5.3.1.4-9	Development and validation of an immunogenicity method with improved drug tolerance for the determination of anti-ACZ885 antibodies in human serum Method description and validation Amendment No. 1	ノバルティス	2016年1月15日	フランス，計1施設	海外	社内報告書	参考
5.3.2　ヒト生体試料を用いた薬物動態関連の試験報告書【該当資料なし】							
5.3.3　臨床薬物動態（PK）試験報告書							
5.3.3.1　健康被験者におけるPK及び初期忍容性試験報告書【該当資料なし】							
5.3.3.2　患者におけるPK及び初期忍容性試験報告書【該当資料なし】							
5.3.3.3　内因性要因を検討したPK試験報告書【該当資料なし】							
5.3.3.4　外因性要因を検討したPK試験報告書【該当資料なし】							
5.3.3.5　ポピュレーションPK試験報告書							
5.3.3.5-1	Population pharmacokinetics of canakinumab (ACZ885) in patients with Periodic Fever Syndromes (crFMF, HIDS/MKD and TRAPS) Modeling Report	ノバルティス	2016年2月16日	―	海外	社内報告書	参考
5.3.3.5-2	Exploration of the pharmacokinetics and pharmacodynamics of canakinumab (ACZ885) in patients with Periodic Fever Syndromes (crFMF, HIDS/MKD and TRAPS) Modeling Report	ノバルティス	2016年2月9日	―	海外	社内報告書	参考
5.3.4　臨床薬力学（PD）試験報告書【該当資料なし】							

添付資料番号	表 題	著者	試験実施期間	試験実施場所	報種類（国内／海外）	掲載誌	評価／参考
5.3.5　有効性及び安全性試験報告書							
5.3.5.1　申請する適応症に関する比較対照試験報告書							
5.3.5.1-1	A randomized, double-blind, placebo controlled study of canakinumab in patients with Hereditary Periodic Fevers (TRAPS, HIDS, or crFMF), with subsequent randomized withdrawal/ dosing frequency reduction and open-label long term treatment epochs	ノバルティス	2014年6月27日～進行中（Week 16の最終観察日：2015年8月25日）	ベルギー，カナダ，フランス，ドイツ，ハンガリー，アイルランド，イスラエル，イタリア，日本，オランダ，ロシア，スペイン，スイス，トルコ，イギリス，米国，計61施設	国際共同	社内報告書	評価
5.3.5.2　非対照試験報告書							
5.3.5.2-1	An open-label, multicenter, efficacy and safety study of 4-month canakinumab treatment with 5-month follow-up and long-term treatment period in patients with active recurrent or chronic TNF-receptor associated periodic syndrome (TRAPS)	ノバルティス	2010年10月27日～2014年6月20日	アイルランド，イタリア，イギリス，計6施設	海外	社内報告書	参考
5.3.5.2-2	A 6 month phase 2, multi-Center, Open-label, siNgle arm study To evaluate the safety and efficacy of tReatment with canakinumab (Ilaris) in pediatric patients with cOLchicine intolerant or colchicine resistant Familial Mediterranean Fever – CONTROL FMF – study	ノバルティス	2010月12月29日～2012年2月26日	イスラエル，計4施設	海外	社内報告書	参考
	errata list						
5.3.5.2-3	An open-label, multicenter, efficacy and safety pilot study of 6-month canakinumab treatment with up to 6-month follow-up and 24-month long-term treatment in patients with active Hyper-IgD Syndrome (HIDS)	ノバルティス	2011年3月24日～2014年7月15日	スペイン，計3施設	海外	社内報告書	参考
5.3.5.2-4	An open-label, exploratory study to establish the safety and efficacy of 3 months treatment with canakinumab in subjects with colchicine resistant Familial Mediterranean Fever	ノバルティス	2010年12月31日～2011年10月25日	トルコ，計1施設	海外	社内報告書	参考
	errata list						
5.3.5.3　複数の試験成績を併せて解析した報告書							
5.3.5.3-1	SCS Appendix 1 (Integrated Summary of Safety, data analyses)	ノバルティス	－	－	海外	社内報告書	参考
5.3.5.3-2	SCS Appendix 2 (Deaths and SAEs in Ongoing Studies)	ノバルティス	－	－	海外	社内報告書	参考

添付資料番号	表 題	著者	試験実施期間	試験実施場所	報種類（国内／海外）	掲載誌	評価／参考
5.3.5.4　その他の臨床試験報告書							
5.3.5.4-1	An open-label, efficacy and safety study of canakinumab (anti-interleukin-1β monoclonal antibody) administered for 6 months (24 weeks) in Japanese patients with the following cryopyrin-associated periodic syndromes: Familial Cold Autoinflammatory Syndrome, Muckle-Wells Syndrome, or Neonatal Onset Multisystem Inflammatory Disease, followed by an extension phase to provide canakinumab to study patients until it is approved for marketing in Japan	ノバルティス	2009年10月19日～2012年2月29日	日本，計3施設	国内	社内報告書	参考
	Amendment 1 to CACZ885D2308	ノバルティス	2009年10月19日～2012年2月29日	－	国内	社内報告書	参考
	ACZ885D2308 Note to File						
	errata list						
5.3.5.4-2	A multi-center, open label, 24-month treatment study to establish the safety, tolerability, efficacy, pharmacokinetics and pharmacodynamics of canakinumab (anti-IL-1 beta antibody) in patients with NOMID / CINCA syndrome	ノバルティス	2009年1月26日～2011年2月17日	米国，計1施設	海外	社内報告書	参考
5.3.5.4-3	Canakinumab treatment of a patient with severe HIDS	[redacted]病院	2013年5月～2017年4月又は当該適応症の承認日のいずれか早い期日まで	日本，計1施設	国内	社外報告書	参考
5.3.6　市販後の使用経験に関する報告書							
5.3.6-1	PERIODIC SAFETY UPDATE REPORT 12 (PSUR 12)	ノバルティス	Period covered: 2015年1月1日～2015年6月30日	－	海外	社内報告書	参考
5.3.6-2	第6回安全性定期報告	ノバルティス	Period covered: 2014年1月1日～2014年12月31日	－	国内	社内報告書	参考
5.3.7　患者データ一覧表及び症例記録							
5.3.7-1	症例一覧表	ノバルティス	－	－	国内	社内報告書	参考
5.3.7-2	副作用一覧表						
5.3.7-3	重篤な有害事象一覧表						
5.3.7-4	臨床検査値の異常変動一覧表						
5.3.7-5	臨床検査値推移図						

添付資料番号	著者・表 題・掲載誌	報種類（国内／海外）
5.4 参考文献　（評価／参考の別：参考資料）		
5.4-1	Aganna E, Hammond L, Hawkins PN, et al. (2003) Heterogeneity among patients with tumor necrosis factor receptor-associated periodic syndrome phenotypes. Arthritis Rheum; 48(9):2632-44.	海外
5.4-2	Arlet JB, Le Thi Huong D, Marinho A, et al. (2006) Reactive haemophagocytic syndrome in adult-onset Still's disease: a report of six patients and a review of the literarture. Ann Rheum Dis; 65:1596-601.	海外
5.4-3	Choy E and Sattar N (2009) Interpreting lipid levels in the context of high-grade inflammatory states with a focus on rheumatoid arthritis: a challenge to conventional cardiovascular risk actions. Ann Rheum Dis; 68:460-9.	海外
5.4-4	Dascombe MJ, Rothwell NJ, Sagay BO, et al (1989) Pyrogenic and thermogenic effects of interleukin 1 beta in the rat. Am J Physiol.; 256:E7-11.	海外
5.4-5	Dinarello CA (2005) Interleukin-1β. Crit Care Med; 33(12) Suppl: S460-S462.	海外
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5.4-7	Hull KM, Drewe E, Aksentijevich I, et al. (2002) The TNF receptor-associated periodic syndrome (TRAPS): emerging concepts of an autoinflammatory disorder. Medicine (Baltimore); 81(5):349-68.	海外
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5.4-9	Lachmann HJ, Papa R, Gerhold K, et al. (2014) The phenotype of TNF receptor-associated autoinflammatory syndrome (TRAPS) at presentation: a series of 158 cases from the Eurofever/EUROTRAPS international registry. Ann Rheum Dis.; 73(12):2160-7.	海外
5.4-10	Livneh A, Langevitz P, Zemer D, et al. (1997) Criteria for the diagnosis of familial Mediterranean fever. Arthritis Rheum; 40(10):1879-85.	海外
5.4-11	Onen F (2006) Familial Mediterranean fever. Rheumatol Int.; 26(6):489-96.	海外
5.4-12	Piram M, Frenkel J, Gattorno M, et al. (2011) A preliminary score for the assessment of disease activity in hereditary recurrent fevers: results from the AIDAI (Auto-Inflammatory Diseases Activity Index) Consensus Conference. Ann Rheum Dis.; 70(2):309-14.	海外
5.4-13	Rosenwasser LJ (1998) Biologic activities of IL-1 and its role in human disease. J Allergy Clin Immunol; 102:344-50.	海外
5.4-14	Sawhney S, Woo P, Murray KJ (2001) Macrophage activation syndrome: a potentially fatal complication of rheumatic disorders. Arch Dis Child; 85:421-6.	海外
5.4-15	Stephan JL, Kone-Paut I, Galambrun C, et al. (2001) Reactive Haemophagocytic syndrome in children with inflammatory disorders. A retrospective study of 24 patients. Rheumatology (Oxford); 40:1285-92.	海外
5.4-16	ter Haar N, Lachmann H, Özen S et al. (2013) Treatment of autoinflammatory diseases: results from the Eurofever Registry and a literature review. Ann Rheum Dis.; 72(5):678-85.	海外
5.4-17	ter Haar NM, Oswald M, Jeyaratnam J, et al. (2015) Recommendations for the management of autoin-flammatory diseases. Ann Rheum Dis; 74(9):1636-44.	海外
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5.4-20	酒井秀政, 平家俊男 (2011) 日本における高IgD症候群の診断と展望. Jpn. J. Clin. Immunol; 34(5):382-7.	国内
5.4-21	増本純也 (2011) インフラマソーム. Jpn. J. Clin. Immunol.; 34(5):346-54.	国内
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